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STUDIES OF DISEASES OF THE LYMPHOID AND MYELOID TISSUES.

VII. THE NUCLEOTIDE THERAPY OF AGRANULOCYTIC ANGINA, MALIGNANT NEUTROPENIA AND ALLIED CONDITIONS.

AN ANALYSIS OF 69 CASES.*

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IN a preliminary paper[1] we reported the results of the treatment of 20 cases of agranulocytic angina and other forms of malignant neutropenia of varied etiology by the intravenous and intramuscular injections of pentose Nucleotide K96.† We use the term agranulo-

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cytic angina to cover those cases in which, without known etiology, there is extreme lowering of the white blood cell count and polymorphonuclear neutrophils. The condition is usually acute and there are generally pronounced ulcerative lesions in the mouth or other mucous membranes. We use the term malignant neutropenia in this paper to cover those cases in which extreme leukopenia has followed a definite septic process as, for instance, pneumonia or pansinusitis. The etiology of the two types of neutropenia appears to be different; the prognosis the same.

Since our preliminary publications[1] there have been treated, adequately, 49 additional cases, making a total of 69. Of these 69, 51 (74 per cent) completely recovered. In the most recent analysis of this type of case Taussig and Schnoebelin found that only 25 per cent of 328 collected cases recovered without special therapy;[2] these authors, after excluding those cases which terminated fatally within 48 hours of the time treatment was instituted, found that 47 per cent recovered when treated by Roentgen ray, 37 per cent when treated with blood transfusion and 27 per cent when given arsphenamin. They also found that only 25 per cent of 178 cases recovered following miscellaneous forms of treatment.

We are greatly indebted to the various physicians under whose care these cases were at the time of their treatment. Without their coöperation, this report would not be possible.

A brief analysis of our own results following the use of Nucleotide K96 is presented.

Patients who died less than 72 hours after treatment was begun, or those in whom treatment was discontinued within this period, have been excluded from this report. A similar selection has been practised by other investigators. Those patients who received only a very brief treatment and then recovered were also excluded because we believed that the treatment was too short to have effected the improvement seen. The preparation was also used in a number of cases of idiopathic aplastic anemia or leukemia. These cases are not included, as the material appears to be of no value in these diseases.

Of the 69 adequately treated cases, 54 were typical agranulocytic angina. Of these 54, 38 (70 per cent) recovered and are to date well. Seven of these cases relapsed after a period of weeks or months but again responded as before to a second treatment with Nucleotide K96. Two cases (Nos. 13b and 39), died in fulminating relapses. In our statistics a recovery is ascribed but once to a case, no matter how many times it may have relapsed and again responded. A case responding favorably once but dying in a subsequent relapse is counted as a death only.

The time and type of response was similar in most cases. The consistency with which hematologic improvement occurred about the fifth day, as recorded in our first paper,[1] has been borne out by

the observations on the additional 49 cases. In 74 per cent of the cases responding, whether agranulocytic angina or sepsis with leukopenia, the white blood cell count began to rise on the fourth, fifth or sixth days following the initiation of treatment, irrespective of the duration of the illness prior to treatment (Chart I), and it continued

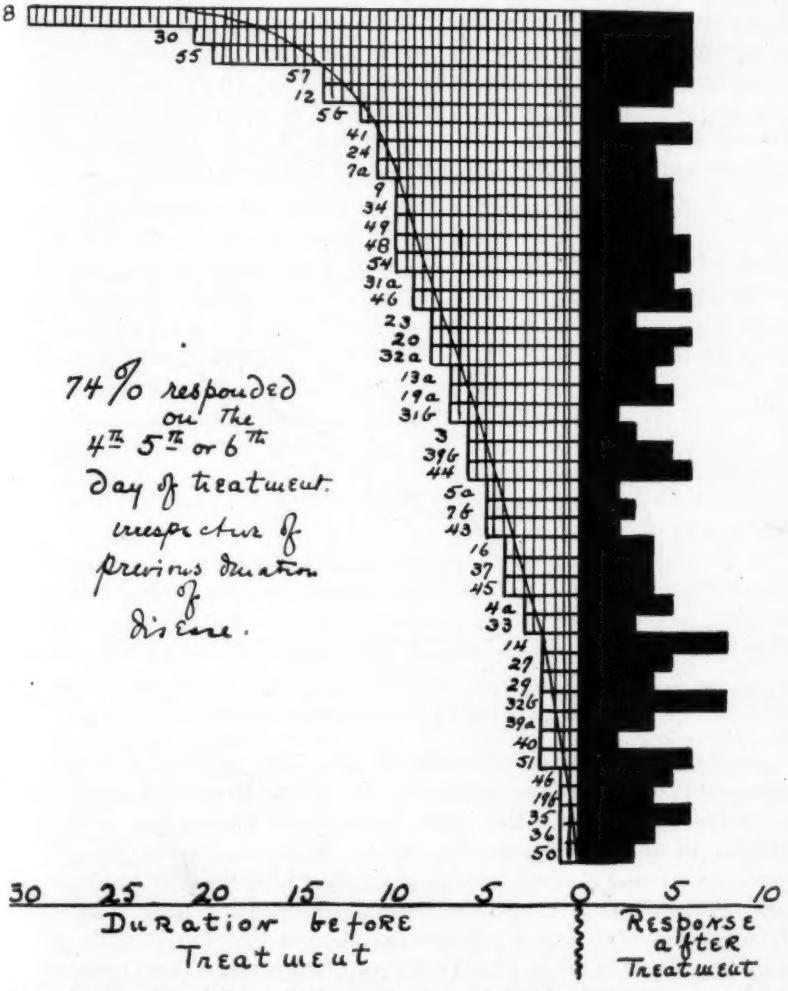

CHART I.—Duration of disease before treatment and time of response after treatment in days.

to rise uninterruptedly from that time on until a high normal figure had been reached, as a rule on or about the tenth day of Nucleotide therapy. If the median white blood cell count for all cases be charted, it is seen that the rise occurs sharply on the fifth day (Chart II). In cases very carefully studied it was usually noted that

a few young polymorphonuclear neutrophils appeared within 48 hours. Unequivocal improvement was usually somewhat later and it is to this pronounced improvement that we refer. The constancy with which improvement began about the fifth day of treatment, irrespective of the duration of the disease, we believe to be an important indication of the effectiveness of the product. In each instance the illness was dated from the beginning of continuous symptoms, although in several cases temporary premonitory symptoms had been present weeks before (No. 41). In virtually all cases the temperature fell to normal a day or so after the first definite rise of white blood cells. Only rarely was there a temporary elevation of temperature once a normal level had been reached.

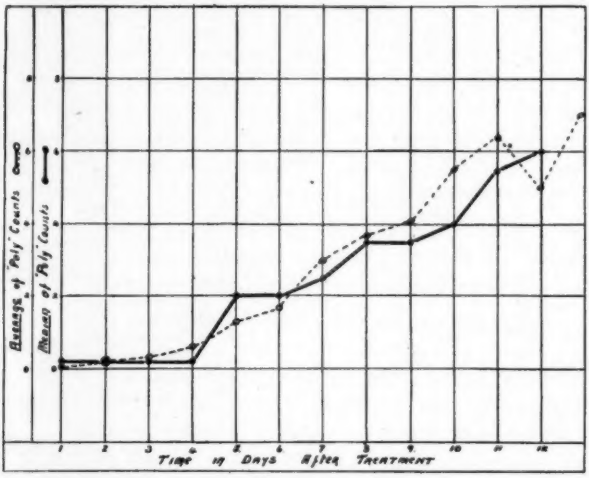

CHART II.—Median and average polymorphonuclear neutrophil counts of all cases from the beginning of treatment to recovery.

In 1 case of agranulocytic angina (No. 19a), pyelitis with pus in the urine developed suddenly as the white blood cell count approached normal and the same sequence of events was seen in a relapse of the same case (No. 19b). In another case (No. 27) a periappendiceal abscess developed as the white blood cell count rose and the abscess was then successfully drained. In a third case (No. 35) a very large ischiorectal abscess developed with great rapidity after the white blood cell count had reached 6000 per c.mm., and in another (No. 31) suppuration of the cervical lymph nodes took place during early convalescence. Appropriate treatment, often surgical, should be instituted for these complications which are, in a sense, signs of impending recovery. In some instances surgical intervention may be of the greatest importance in removing the source of infection. In 3 of these cases with suppurative complications, there was a sharp temporary drop in the white blood cell count at the time the complication arose, followed by an equally

rapid resumption of the previous upward trend of the white blood cell count. Our interpretation of these findings is that the complicating lesions were present before the obvious local signs were manifest, but that in the absence of polymorphonuclear cells the usual inflammatory response could not take place until the bone marrow had at least partially recovered. That the late infections, in and by themselves, caused the rise in white blood cell count is militated against both by the fact that in 3 instances the white blood cell count was already markedly increased and that in all cases other ulcerative lesions were manifest (without pus formation) from the beginning of the disease and yet they did not cause any increase in white blood cells.

Of the agranulocytic angina cases 87 per cent were females; 2 cases were in the 1st decade of life, 3 in the 2d, 9 in the 3d, 11 in the 4th, 11 in the 5th, 17 in the 6th, 9 in the 7th and 3 in the 8th.

The average duration of the disease before the institution of Nucleotide treatment was 7.2 days. Unquestionably the initiation of therapy earlier in the disease would further decrease the mortality, although certain fatal cases as No. 47 in which treatment was begun the moment the disease was suspected, are so fulminating that no treatment at present available would probably be successful. This patient died on the morning of the 4th day of the disease.

In addition to the 54 cases of idiopathic agranulocytic angina, 13 cases of sepsis followed by extreme leukopenia and neutropenia, were treated. Of these, 11 (84 per cent) recovered promptly and completely. The sepsis was of various sorts: pansinusitis (No. 12), infected arteriosclerotic gangrene (No. 51), infantile pneumonia (Nos. 3 and 4). The mode of recovery and the time of the first rise of the white blood cell count in this type of case were identical with those seen in the idiopathic agranulocytic angina cases.

One case responded sharply and characteristically to the first treatment and then over a period of several months had a series of relapses each of which responded temporarily to Nucleotide therapy. Eventual recovery followed another form of treatment so that the case is not included in this series of 69.

Two cases of very severe benzol poisoning were treated. These have already been discussed in our preliminary paper.[1] Case No. 1 was discharged from the hospital September 1, 1931, with a white blood cell count of 4500 per c.mm. Without any especial treatment the white blood cell count remained constantly at this figure until November 1, 1931. The patient was then readmitted and given, intramuscularly, 10 cc. Nucleotide K96 daily for 2 weeks. At the end of this period of treatment the white blood cell count had risen to 8500 per c.mm. and it has remained at approximately this level for the past 5 months. Case No. 2 is entirely well. In each patient a rise of white blood cell count was seen every time Nucleotide K96 was given as noted in the preliminary report.

Many physicians apparently feel that patients with agranulocytic angina or malignant neutropenia and sepsis who have a white blood cell count above 1000 per c.mm. have a much better chance of recovery than those in whom it is below 1000 per c.mm. Of our 69 cases, 33 (48 per cent) had before treatment a white blood cell count of 1000 per c.mm. or less. Of these 33 patients 66.6 per cent recovered as against 74 per cent recoveries in the entire reported series. Of our cases 10 (15 per cent) had white blood cell counts of 500 per c.mm. or below, yet of these 60 per cent recovered. Again the prognosis is often believed to be increasingly poor in cases which have no polymorphonuclear neutrophils. Of our patients 38 (55 per cent) showed a complete absence of polymorphonuclear neutrophils before treatment, yet 76.3 per cent of these recovered. In only 3 of the entire series of cases was the maximum temperature below 102° F. In 26 cases the highest temperature was 105° F. or over. In 1, No. 57, the temperature reached 106.5° F., yet the patient recovered. Of these cases whose temperature reached 105° F. or over, 65 per cent recovered.

Thus very low white blood cell counts, complete absence of polymorphonuclear neutrophils and very high temperatures do not materially affect, in this series at least, the prognosis.

As the series has become larger it has become increasingly obvious that medication, to be effective, must be intensive and continuous. Of the Nucleotide K96 preparation 10 cc. (equivalent to 0.7 gm. of the solid), should be injected intramuscularly twice a day until the white blood cell count has very definitely risen; 10 cc. should then be given intramuscularly once a day until the white blood cell count has been essentially normal on at least 3 consecutive days. Thereafter the patient should be watched for a possible relapse. In certain resistant cases an increase over the usual dose brought a marked increase of white blood cells, after smaller doses had produced little or no effect (Nos. 30 and 51). In desperately ill cases the contents of one vial should be diluted to 100 cc. with warm sterile saline and injected slowly intravenously each morning for 4 days. On the evening of each of the same days, 10 cc. (undiluted) should be injected intramuscularly. At the end of 4 days the intravenous injections may be discontinued but the bi-daily intramuscular injections should be kept up until the white blood cell count has definitely risen, after which daily single intramuscular injections are to be continued until the white blood cell count has been at a normal figure for at least 3 consecutive days.

To the intramuscular injections there are, as a rule, few if any unfavorable reactions attributable to the material. An occasional patient may have nausea, precordial distress and dyspnea, immediately following an injection. Rarely there may be chills and fever several hours later, but we believe that an improved method of preparing the material has largely eliminated these features. To

the intravenous injections there is usually an immediate reaction of dyspnea and palpitation and in an occasional case there may be chills and fever several hours after the injection. The intravenous injection should, therefore, not be used in the presence of myocardial damage.

No improvement is to be expected during the first few days of treatment. In fact the patient may appear to become worse. This is no indication that eventual recovery will not take place and is no reason for discontinuing treatment. The white blood cell count may even fall during the early days of treatment but this fall can be attributed to progress of the disease occurring before the Nucleotide can sufficiently effect the production of white blood cells.

Relapses occurred in 17 per cent of the agranulocytic angina cases and one must be ready to resume intensive Nucleotide treatment if such do occur. If the white blood cell count rises and then, while still under treatment, starts to fall, an increase of dosage is indicated and favorable results may be expected as in Case No. 51.

We believe that no other specific therapy should be instituted during Nucleotide treatment and that only mild local medication is necessary. The continuous swabbing of the lesions with a variety of antiseptics serves only to disturb the patient. The real problem is that of raising the white blood cell count. Careful nursing care, abundance of fluids and as much nourishment as possible are obvious parts of the treatment. Daily white blood cell counts and careful differential counts should be made. Only thus may the course of the disease be adequately followed. Transfusions of blood in our experience have been more detrimental than beneficial. That they may do good in certain cases is not denied but the evidence in favor of this hypothesis is not striking.

As to etiology, we believe that there are 2 classes of malignant neutropenia. First, there is the primary type in which the leukopenia may precede any symptoms by several days (No. 35). In this case the white blood cell count was for 3 successive days at an approximate level of 500 cells per c.mm. and yet the patient felt perfectly well and was at her work. Routine white blood cell counts were done on this patient because she was known to have had several previous attacks of agranulocytic angina. Only on the evening of the 3d day of leukopenia did the temperature suddenly rise to 104° F. and sore throat develop. The progress of this case strengthens our previous opinion that in true agranulocytic angina of the idiopathic type the blood changes precede and condition the striking anginal symptoms. Second, there is the secondary type in which some obvious infection brings about gradual or rapid fall in the white blood cell count. This latter type is seen following osteomyelitis, pansinusitis, liver abscess, pneumonia or staphylococcus septicemia. The prognosis in the two types appears to be the same; equally grave without appropriate treatment; equally

favorable in this series treated with Nucleotide K96. The etiology of such toxic leukopenias as those induced by benzol or arsenic is obvious.

Summary and Conclusions. An analysis of 69 cases of malignant neutropenia treated with pentose Nucleotide K96 is presented; 74 per cent recovered.

That the preparation was, in fact, effective we believe because:

1. The favorable clinical and hematologic response took place rather sharply about the 5th day of treatment, irrespective of how long the patient had been ill prior to treatment.
2. The subsequent hematologic improvement in practically all cases followed the same orderly pattern.
3. The mortality is the lowest of any published series of like size.
4. Certain laboratory studies, to be reported on at a later date, support the clinical data.

NOTE.—These cases were treated by 40 different physicians in 12 different states. Without their kind coöperation the series could never have been attained. We are particularly indebted to Drs. F. T. Hunter of the Massachusetts General Hospital and W. P. Thompson of the Presbyterian Hospital, New York. The following physicians have contributed to the reported series and we wish to express our appreciation of their coöperation. Boston: J. Baty, M. Blair, F. T. Hunter, R. Lee, F. Newton, W. Dameschek, G. Schwartz; Cleveland: W. Payne; Columbus: C. Doane; Denver: W. C. Black; Evanston, Ill.: F. Burcky; Chicago: H. L. Alt; Hartford: J. W. Hutchison; Lewiston, Maine: J. Gottlieb; Milwaukee: B. J. Birk, W. M. Egan; New Haven: W. W. Bunnell, S. J. Goldberg, A. W. Oughterson; New York: J. Lintz, H. Manley, C. Reich, N. Rosenthal, W. P. Thompson, M. J. Stone; Philadelphia: J. Reisinger; Wilkes-Barre: A. R. Feinberg; Portland, Maine: M. Warren; Providence: F. T. Fulton; Rochester, N. Y.: D. Jewett; San Francisco: L. R. Chandler, E. Falconer; Waterbury, Conn.: J. H. McGrath; Youngstown, Ohio: C. Clarke; Richmond-Highlands, Washington: E. J. Lewis.

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THE RESPONSE OF RETICULOCYTES TO POTENT DIETS IN SEVERE EXPERIMENTAL ANEMIA DUE TO HEMORRHAGE.

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THE appearance of reticulated red blood cells in the peripheral circulation has for several years been a matter of considerable clinical interest. Investigation has indicated that definite increase

in reticulocytes may be obtained following liver and iron therapy in posthemorrhagic anemias.[6,3]

This paper reports the results of a study of the reticulocyte response to potent diets in carefully controlled experimental anemias. The animals used are highly standardized dogs, suffering from a severe anemia existing for a period of years due to blood removal.

Methods. The present experiments were carried out on dogs which are being used for the study of hemoglobin and red cell regeneration. The general experimental procedures to which these animals are subjected have been described before.[5]

The experimental animals were born and raised in our kennels and are kept under practically constant conditions with regard to exercise, ventilation and uniform temperature in the dog rooms. The dogs are rendered anemic by four or more bleedings spaced at 1- or 2-day intervals. The desired anemia level of 40 to 50 per cent hemoglobin is then maintained as near a constant as possible by further hemorrhages graded as to frequency and amounts. Some of the hemoglobin values recorded on the tables may appear as high ones. These high figures, however, represent the levels just prior to further removal of blood in order again to reach the desired anemia level. Blood plasma volume determinations are essential since fluctuations of plasma volume must be taken into consideration in estimating the required bleeding. Hemoglobin pigment in grams is determined in every aspirated bleeding. Hemoglobin is measured in the form of acid hematin colorimetrically against a standard which at 100 per cent is equivalent to 13.8 gm. of hemoglobin per 100 cc. The animals are kept on a standard basal ration consisting of a bread mixture prepared in the laboratory. This basal ration bread is adequate to maintain the anemic dog in health for years and yet permits of but minimal hemoglobin and red cell regeneration over and above the maintenance factor. This bread ration is used in the control periods alternating with or combined with other food factors or drugs to be tested. The animals used in this experiment belong to this carefully standardized anemic colony and their response to various diets is well known. The degree of regeneration is measured by the amount of hemoglobin produced each week over and above the maintenance factor. This maintenance factor indicates the hemoglobin and red cells used up by the general wear and tear of the circulation in the body. We also speak of a "carry over." By this is meant that a dog on a favorable diet will store somewhere in its tissues or organs the ingredients for hemoglobin and red cell construction which later during unfavorable diet periods will be drawn upon for the manufacture of hemoglobin and red cells.

It must be emphasized that the bone marrow is under sustained maximal stimulation because of the long existing anemia and repeated bleedings. The diet is adequate for general maintenance requirements. There were no complicating factors of an infectious or toxic nature. After the control period on the standard bread diet lasting 2 or more weeks, diets known to be very potent for hemoglobin regeneration were fed during a 2-week period which was again followed by the control basal bread ration. In one case, iron was administered intravenously. Daily reticulocyte and erythrocyte counts were made in addition to the usual weekly sampling and blood volume determinations, all blood being obtained by jugular puncture. For reticulocyte counts, the wet method was used. As the blood flowed freely from the needle in the jugular vein, a small drop was rapidly transferred on the tip of a glass rod to a cover-slip. The cover-slip was then gently inverted on a slide on which a film of 0.5 per cent alcoholic solution of brilliant cresyl blue had been dried. The preparation was rimmed with

vaseline and the number of reticulocytes in 1000 red cells were counted under oil immersion. Care was taken to count all of the cells in several different areas of the slides in order to avoid errors due to clumping of reticulocytes. The number of reticulocytes per cubic millimeter of blood can be readily calculated from the total red blood cell count and the reticulocyte per cent.

Dry Method. Permanently stained smears, using the method of Hawes[1] and Cunningham,[2] were made in one series of experiments. It was found that the cells failed to stain well with the brilliant cresyl blue. A satisfactory explanation of this has not as yet been found. It is possible that the cells did not remain sufficiently long in contact with the dye, before the smear was pulled. Increased speed of coagulation necessitated immediate pulling of smears. Citrated blood was not used. There is a possibility that there is some change in the permeability of the red cells of the anemic dog. They are known to be much less fragile than the normal. Because of the discrepancies in the results obtained by the dry method, they are not included in this paper.

Experimental Data. The blood picture, in general, presented by these animals is that of an extreme, secondary anemia, with aniso- and poikilocytosis and erythrocytes of very small diameter. Microcytes and what appear to be cell fragments are also present in large numbers. The reticulocytes vary from large pale cells to cells of very small size. The reticulum is often very dense, as noted by Seyfarth in anemias with rapid regeneration.[4] Normoblasts appear very rarely.

The blood platelets present an extremely interesting picture. They attain an enormous size, approximating in many cases the diameter of a normal erythrocyte. They appear singly or grouped in clusters. In certain instances these platelets are present in extraordinarily large numbers, particularly in Dog 27-241, Table 3.

The detailed observations are recorded in Tables 1 to 6 and show certain points which are worthy of emphasis. In each dog the total red blood cell curve does not parallel the hemoglobin curve, the rise in red blood cell not being proportional to the amount of hemoglobin.

Dog 25-97. This animal has been raised on a liver diet since weaning and has always responded much more actively with hemoglobin regeneration to any diet than the usual anemic dogs. This experiment demonstrates a high reticulocyte level during the control period when hemoglobin regeneration is low. The pre-control period was preceded by a potent dietary régime with much hemoglobin production. When the animal is put on liver and iron which constitutes one of the most potent hemoglobin-building diets the reticulocyte response is only a questionable one. The hemoglobin production during this two-week test diet period amounts to 63 gm. over and above the maintenance level. The total hemoglobin output due to the liver and iron feeding is figured as approximately 120 gm. in this experiment.

The actual reticulocyte per cent increase is but 20 per cent whereas the reticulocyte concentration (red cells x per cent reticulocytes)

shows a rise of 48 per cent. No acute response of reticulocytes follows the various bleedings. When the dog is again placed on the control diet, one notices a definite drop in reticulocytes which reaches a lower level than that during the previous control period. This occurs in spite of a carry over of hemoglobin production of 56 gm.

TABLE 1.—LIVER AND IRON (DOG 25–97, BULL, FEMALE, ADULT).

Diet, Grams per day.	Date.	Reticulocytes.		R. B. C.	Hb. removed by bleeding.	Hb. level.	R. B. C. vol. hematokrit.	Plasma vol.
		Thousands per c.mm.	Per cent.	Millions per c.mm.	Gm.	Per cent.	Per cent.	Cc.
Bread (S) 450*	July 11	255	4.9	5.2	1.4	49	21.5	1177
	12	210	4.5	4.7				
Liver 300	13							
Fe. 40 mg.	14	323	6.6	4.9				
Bread (S) 400	15	...	4.0					
	16	140	3.1	4.5				
	17	143	2.8	5.1				
	18	222	3.9	5.7	....	69	30.6	1058
	19	260	4.0	6.5	16.5			
	20							
	21	204	3.0	6.8	17.5			
	22	180	3.1	5.8	12.3			
	23	125	3.3	3.8				
	24	243	4.2	5.8	....	67	30.6	
	25	213	3.8	5.6	....	71	30.7	1034
	26	297	5.4	5.5	17.0			
Bread (S) 450*	27							
	28	155	3.1	5.0	16.6			
	29	69	1.5	4.6	11.2			
	30	100	2.0	5.0				
	31	143	2.7	5.3	....	67	28.3	
	Aug. 1	141	3.0	4.7	....	62	27.3	1075
	2	105	2.3	4.6	16.7			
	3							
	4	103	2.4	4.3	11.4			
	5	70	2.0	3.5				
	6	121	3.2	3.8	....	52	22.4	
	7	144	3.9	3.7				
	8	138	3.3	4.2	....	45	19.5	1124
	9	140	3.6	3.9				

* Salmon 75, Klim 25.

Table 2 depicts another experiment of liver and iron feeding. The reticulocyte level during the control bread period is considerably below that presented by other dogs of this experimental series.

Dog 24–45 demonstrates a definite reticulocyte response on the 6th day of the potent diet feeding, increasing to 5.8 per cent or a reticulocyte concentration of from the beginning average of 55,000 to 325,000 on the liver and iron diet. This constitutes about a 500

per cent increase in reticulocyte concentration. This result is in marked contrast to the previous experiment, Table 1. Six days later there is another rise to 4 per cent or 264,000 reticulocytes per c.mm. with a subsequent drop to the control level.

TABLE 2.—LIVER AND IRON (DOG 24–45, BULL, FEMALE, ADULT).

Diet, Grams per day.	Date.	Reticulocytes.		R. B. C.	Hb. removed by bleeding.	Hb. level	R. B. C. vol. hematokrit.	Plasma vol.
		Thous. per c.mm.	Per cent.	Millions per c.mm.	Gm.	Per cent.	Per cent.	Cc.
Bread (S) 500*	July 7	...	...	4.7	18.8	45	19.5	1228
	14	68	1.4	4.9	....	47	20.3	1256
	15	43	1.1	3.9				
Liver 300	16	33	1.0	3.3				
Fe 40 mg.	17	37	1.1	3.4				
Bread (S) 300*	18	31	0.9	3.4				
	19	59	1.5	3.9				
	20							
	21	325	5.8	5.6	....	66	27.9	1155
	22	211	4.4	4.8	15.1			
	23	129	3.0	4.3	15.1			
	24	215	3.9	5.5				
	25	75	1.7	4.4	....	58	25.5	
	26	79	1.8	4.4				
	27							
	28	264	4.0	6.6	....	90	38.9	1068
	29	70	1.3	5.4	20.5			
Bread (S) 500*	30							
	31	92	1.7	5.4	18.9			
	Aug. 1	39	0.9	4.3	17.0			
	2	17	0.4	4.2	....	56	24.3	
	3							
	4	17	0.4	4.2	....	59	24.9	1180
	5	25	0.6	4.1	13.9			
	6	65	1.5	4.3	11.5			
	7	29	0.9	3.2				
	8	26	0.8	3.3	....	47	21.7	

* Salmon 75, Klim 30.

Dog 27–241 shows the result of the feeding of liver. The reticulocytes again are high in the control bread period which in this case has not been preceded by a potent-hemoglobin regenerating diet. They average 280,000 per c.mm. and 5.45 per cent in spite of low hemoglobin production. On the liver diet there is a marked response lasting 3 days, rising to 676,000 and 11 per cent. This constitutes a reticulocyte concentration increase of 130 per cent. During the second control period there is a drop in reticulocytes to below the initial level, although there is a carry over of hemoglobin production.

We again observed a high reticulocyte count in the first control period and there is considerable variation from day to day, the average for the period being 163,200 per c.mm. and 4 per cent.

With addition of the secondary anemia liver fraction W-635, potent for hemoglobin regeneration, to the diet there is only a questionable reticulocyte response beginning on the 4th day and continuing throughout the period with considerable daily variation. This response is more significant in relation to the drop in the second control period, than it is with relation to a rise after the first.

TABLE 3.—LIVER (DOG 27–241, COACH, FEMALE, ADULT).

Diet, Grams per day.	Date.	Reticulocytes.		R. B. C.	Hb. removed by bleeding.	Hb. level.	R. B. C. vol. hematokrit.	Plasma vol.
		Thous. per c.mm.	Per cent.	Millions per c.mm.	Gm.	Per cent.	Per cent.	Cc.
Bread (S) 325*	June 27	...	....	4.9	....	42	19.5	820
	July 2	258	4.7	5.5				
	3	285	5.6	5.1	....	47	22.2	860
	4	312	5.9	5.3				
	5	296	5.6	5.3				
Liver A-924-230	6	557	8.7	6.4				
Bread (S) 325*	7	550	11.0	5.0				
	8	676	10.9	6.2				
	9	324	5.6	5.8				
	10	383	6.5	5.9				
	11	233	3.5	6.7	....	70	31.5	787
	12	288	4.0	7.2	18.3			
Bread (S) 325*	13							
	14	240	4.0	6.0	19.3			
	15	212	5.6	3.8				
	16	190	3.8	5.0	....	61	27.0	
	17	138	3.3	4.2				
	18	131	2.8	4.7	....	53	23.1	805
	19	211	4.6	4.6	13.6			
	20							
	21	181	4.2	4.3	....	50	21.6	
	22	202	4.8	4.2				
	23	184	4.1	4.5				
	24	280	5.1	5.5				
	25	165	3.6	4.6	....	57	23.1	797

* Salmon 100, Klim 30.

Dog 23–1. The reticulocyte level is again seen to be high in the first control period. On the addition of liver, plus a secondary anemia liver fraction plus additional iron to the diet, there is a reticulocyte response which seems definite on the 7th day. The reticulocyte response occurs several days after the active regeneration of hemoglobin had begun. There is again a drop in the reticulocyte level during the second control period. This dog differs from the animals described above in that the drop during the first week of the after control period is less than that during the second week, 3.98 per cent and 2.88 per cent averages, respectively.

TABLE 4.—SECONDARY ANEMIA LIVER FRACTION (DOG 24–2, BULL FEMALE, ADULT)

Diet, Grams per day.	Date.	Reticulocytes.		R. B. C.	Hb. removed by bleeding.	Hb. level	R. B. C. vol. hematokrit.	Plasma vol.
		Thous. per c.mm.	Per cent.	Millions per c.mm.	Grams.	Per cent.	Per cent.	Cc.
Bread (S) 325*	July 2	126	2.8	4.5	11.9	51	23.5	945
	3	175	3.8	4.6				
	4	...	3.5					
	5	126	3.6	3.5	....	46	20.1	
	6	229	5.6	4.1				
	7	118	3.2	3.7				
	8	102	3.0	3.4				
	9	176	4.0	4.4	....	49	22.4	942
	10	253	6.5	3.9				
Sec. anemia fraction†	11	...	3.5					
Bread (S) 325*	12	110	2.9	3.8				
	13							
	14	253	6.5	3.9				
	15	198	4.6	4.3				
	16	196	3.7	5.2	....	59	24.3	939
	17	176	4.0	4.4	12.2			
	18	172	4.3	4.0	12.0			
	19	189	5.4	3.5				
	20							
	21	209	5.5	3.8	....	58	24.2	
	22	176	4.3	4.1				
	23	271	6.6	4.1	....	54	23.5	961
	24	225	4.9	4.6	17.3			
Bread (S) 325*	25	179	4.7	3.8				
	26	129	3.0	4.3	....	58	23.6	
	27							
	28	106	2.8	3.8				
	29	125	3.2	3.9				
	30	...	...	4.7	....	64	26.3	926
	31	167	3.8	4.4	14.9			
	Aug. 1	117	3.9	3.0	10.9			
	2	133	3.8	3.5				
	3							
	4	80	2.5	3.2	....	52	22.5	
	5	131	4.1	3.2				
	6	122	3.6	3.4	....	47	20.2	1016

* Salmon 75, Klim 25.
† 500 gm. fresh liver equivalent.

Dog 27–239. The reticulocyte level in the first control period for 3 days averages 167,000 per c.mm. and 3.67 per cent, which is similar to Dogs 24–2, Table 4 and 23–1, Table 5.

During the administration of iron intravenously there is a definite reticulocyte response which starts on the first day, reaches its maximum on the 4th day amounting to a reticulocyte concentration increase of 167 per cent, continues throughout the test diet

period and carries over into the second control period. The daily variations are of considerable magnitude.

TABLE 5.—LIVER AND SECONDARY ANEMIA LIVER FRACTION PLUS IRON (DOG 23–1, COACH, FEMALE, ADULT).

Diet, Grams per day.	Date.	Reticulocytes.		R. B. C.	Hb. removed by bleeding.	Hb. level.	R. B. C. vol. hematokrit.	Plasma vol.
		Thous. per c.mm.	Per cent.	Millions per c.mm.	Grams.	Per cent.	Per cent.	Cc.
Bread (S) 500*	July 9	...	...	4.7	....	45	20.1	1042
	10							
	11	160	3.9	4.1				
	12	155	3.6	4.3				
Liver 300 Sec. an. fraction‡ Plus Fe. 220 mg.†	13							
	14	317	6.6	4.8				
	15	...	3.3					
	16	161	2.6	6.2	....	60	24.3	995
	17	192	3.7	5.2	13.2			
	18	171	3.8	4.5	12.3			
	19	352	8.0	4.4				
	20							
	21	428	6.8	6.3	....	74	33.0	
	22	221	4.8	4.6				
	23	336	7.0	4.8	....	71	30.2	992
	24	205	3.4	5.9	13.9			
Bread (S) 500*	25	160	3.2	5.0	14.7			
	26	181	4.1	4.4	10.7			
	27							
	28	236	5.9	4.0	....	56	23.2	
	29	108	2.7	4.0				
	30	...	...	...	....	52	22.2	1050
	31	168	3.9	4.3	9.9			
	Aug. 1	119	3.4	3.5				
	2	154	3.5	4.4	....	53	21.7	
	3							
	4	108	2.7	4.0				
	5	53	1.4	3.8				
	6	152	4.0	3.8	....	45	19.2	1095
	7	81	2.3	3.5				

* Salmon 75, Klim 25.
† Bread (S) 350.
‡ 300 gm. fresh liver equivalent.

Following a gradual drop we again observe a rise to 420,000. Another rise occurs on the 3d day of the control period. Unfortunately the reticulocyte counts had to be discontinued before the lower bread control level was reached.

Discussion. Diets potent for hemoglobin regeneration produce but a slight or only moderate reticulocyte response under the experimental conditions reported. Most of these animals show a high

reticulocyte level during the control bread period preceding the test diet régime. One also observes marked individual variations in the reticulocyte response elicited. For example Dog 25–97, Table 1, with a high initial level of reticulocytes was fed an optimum diet for hemoglobin regeneration with the usual result of a very

TABLE 6.—IRON, INTRAVENOUS (DOG 27–239, BULL MONGREL, FEMALE, ADULT).

Diet, Grams per day.	Date.	Reticulocytes.		R. B. C.	Hb. removed by bleeding.	Hb. level.	R. B. C. vol. hematokrit.	Plasma vol.
		Thous. per c.mm.	Per cent.	Millions per c.mm.	Grams.	Per cent.	Per cent.	Cc.
Bread (S) 400*	July 28	...	...	4.2	....	39	18.1	800
	29	116	3.3	3.5				
	30	170	3.7	4.6				
	31	204	4.0	5.1				
Fe, i.v. 20 mg.†	Aug. 1	249	5.3	4.7				
Bread (S) 400*	2	258	6.3	4.1				
	3	490	8.3	5.9				
	4	486	9.0	5.4	....	46	22.1	737
	5	276	5.3	5.2				
	6	209	4.1	5.1				
	7	350	6.6	5.3				
	8	211	3.9	5.4				
	9	255	4.4	5.8				
	10							
	11	234	4.1	5.7	....	68	31.5	725
	12	420	5.6	7.5	14.3			
	13	346	6.3	5.5	14.1			
	14	285	6.2	4.6				
Bread (S) 400*	15	320	6.8	4.7	....	57	26.8	
	16	355	7.1	5.0				
	17	460	9.2	5.0				
	18	...	...	5.6	....	66	30.9	747
	19	...	...	...	16.3			
	20	...	...	...	12.3			
	21							
	22	...	...	...	....	56	24.8	
	23							
	24							
	25	...	...	5.1	....	57	25.3	723
	26	...	...	...	13.6			

* Salmon 75, Klim 25.
† Iron administered as colloidal—Loeser.

high hemoglobin output. As has been mentioned previously this animal has been raised on a diet very rich in liver since weaning and reacts always with much greater hemoglobin manufacture than the other anemic animals of the series. Further stimulation by the liver and iron diet elicits only a very questionable response in reticulocyte output.

Dog 24–45, Table 2, on the other hand, with a much lower reticulocyte level during the control period shows a much more definite reaction to the liver and iron diet as concerns reticulocytes.

If one considers the reticulocyte concentration rather than the percentage rise this increase amounts to 500 per cent in Table 2 as compared to but 48 per cent in Table 1 on the same diet. If one uses this figure for comparison the reticulocyte increases appear to better advantage.

These experiments of course are only a few in number as we were mainly interested in ascertaining whether diets very potent in hemoglobin building properties would also demonstrate a marked increase in the reticulocytes. We observe that in the cases cited feeding the secondary anemia extract gives negative results, adding liver to this diet gives a value just slightly above that of the liver alone. Liver plus iron gave better results than either liver or iron alone. One must remember however that a large series of such experiments may give different results.

One may argue that the red blood cells are at a much higher beginning level than reported in human cases of secondary anemia and that therefore the response would be but a slight one. In considering the bone marrow response of these dogs, however, it must be emphasized that their normal hemoglobin level is approximately 130 to 160 per cent with a red cell count of 8 to 10 millions and that a red cell count of 5 millions in these animals is comparable to one of 3 million in a human being. As the majority of these dogs show red cell figures of 5 million or below at the beginning of the test diet period the anemia level is more severe than one would realize when considering the figure indicated on the tables. These dogs have been kept at an anemia level of one-third of normal for several years. The bone marrow therefore has been under maximal stimulus due to the anemia *per se*, for a long period of time. This is evidenced by the high level of reticulocytes. The added stimulus of a diet, potent in hemoglobin regeneration, does not therefore bring a marked response since stimulus is already nearly maximal. Red cell production might be considered as approaching a normal mechanism in these animals, since there is no toxic factor at work, nor is there any nutritional deficiency. The frequent bleeding masks the level to which the total red blood cell count would rise.

That there is at least some disturbance in the maturation of the erythrocytes, is evidenced, however, by the high control level of reticulocytes. The normal level for dogs is given by Seyfarth[4] as 0.2 to 0.5 per cent. Under the stress of the demand for erythrocytes, the bone marrow turns out some immature cells with the great mass of mature cells. There does not appear to be a correlation between reticulocyte formation and hemoglobin output. The reticulocyte level might be as high with a 10 gm. hemoglobin output as with one amounting to 100 gm. of hemoglobin.

Summary. The response of the reticulocytes on feeding potent diets for hemoglobin regeneration to dogs suffering from a long continued severe anemia produced by blood removal has been compared with the reaction due to the feeding of the basal bread ration. The reticulocyte level shows considerable individual variation. The results obtained demonstrate only a slight or moderate reticulocyte response to diets very potent for hemoglobin regeneration. There seem to be two factors in the potent diets fed. The most important one is the factor influencing hemoglobin regeneration. The second assists in stroma formation.

NOTE.—We gratefully acknowledge the coöperation of Dr. Ethel Simpson MacDonald in preparing the smears for the dry method.

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THE TREATMENT OF SECONDARY ANEMIA WITH "SECONDARY ANEMIA LIVER EXTRACT" AND IRON.*

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DURING the last few years various types of anemias have been investigated extensively, bringing to light new factors in regards their etiology, their classification and their treatment. Whipple may be considered the modern pioneer in this field, and his studies on artificially induced anemias in dogs forms the background for

* We are indebted to Eli Lilly and Company for supplying us with their extract, "Secondary Anemia Liver Extract No. 55 With Iron," which has made this work possible.

most of the recent progress, together with Minot's independent application of a high liver diet in the treatment of Addison-Biermer anemia. Whole liver, kidney, stomach, bone marrow, spleen, extracts of these organs, large doses of iron, and copper have risen rapidly to therapeutic prominence, and one is now confronted with the difficult question of when to use one of these, when to use a combination of them, or whether to use any of them in the treatment of a given case. This confusion in therapy is due to the lack of a satisfactory classification of the anemias, to a lack of standardization as regards a uniformity of dosage, and above all to a wealth of reports on a few interesting cases treated in various ways, but almost no reports on large series of cases treated uniformly and carefully controlled. Under such circumstances it is very difficult to evaluate the various therapeutic agents, consequently only liver and iron, which seem to give the most promise, will be discussed.

A brief review of the work of Whipple and his associates[1] in studying anemias in dogs is essential to an understanding of the basis of liver and iron treatment. He and his co-workers produced a severe anemia in dogs by repeatedly bleeding, which was so regulated as to maintain this anemia at a practically constant level. The intake of iron and the diet could be accurately controlled and also the daily output of iron. Many forms of treatment for these induced posthemorrhagic anemias were tried out.

The findings relative to the use of iron are extremely important and present to a certain degree the key to the success of modern iron therapy. They showed that organic preparations had no value over inorganic ones, and that all inorganic salts were about equally efficacious. Of particular importance is the dosage. Although the animals would eliminate all excess iron over a certain dose, real improvement was often only obtained after giving three or four times this dosage. As it has been long thought that the optimum dosage in man would only be as much as he could utilize, more than this was considered unnecessary. However, Whipple has shown in dogs, at least, that three or four times this dosage is often necessary and then may produce excellent results. The reason for this is not yet understood, but it has been suggested that it is similar to the salt action necessary in certain chemical reactions. There seemed to be no advantage in giving iron subcutaneously or intravenously and the oral method was the one usually chosen. Apparently the problem is one of availability of iron and that if a large amount is present, sufficient will be utilized in the formation of hemoglobin.

These same workers also fed liver to their anemic dogs. They found that whole liver often produced a marked improvement and that an extract of whole liver produced some improvement. Extract of a certain fraction of liver was more effective in treating this hemorrhagic type of anemia than the extract of the whole liver

itself. Finally they found that a combination of liver extract from a fraction of whole liver, which they have designated as a secondary anemia extract, and a large dosage of iron, produced a more brilliant result than all other methods of therapy, except the combination of whole liver and a large dosage of iron. These findings have stimulated extensive clinical investigations along similar lines.

The many clinical reports, however, are not all in accord. A few may be mentioned briefly. Murphy[2] found that liver extract (from whole liver) is of no value in the treatment of secondary anemias. Wahlberg,[3] contributing a study of 19 cases, found that in certain instances liver and liver extract alone seemed effective, and in others they were not effective unless iron was added. Iron alone was most effective in certain instances. Witts[4] has found this true in a group of cases he has designated as achlorhydric, hypochromic anemias. Keefer[5] has reported successful therapy with whole liver extract and iron in secondary anemias. A secondary anemia liver extract has not yet been tried on patients, despite the excellent example of its merit which has been proven in animals.

The object of the present study was to observe the response of various forms of human anemia to a standard secondary anemia liver extract to which iron has been added. We wished to determine the extent of the response, when present; to differentiate the types of anemia which responded, and those which did not; and, if possible to discover any criteria which might indicate if improvement could be expected.

Methods. The cases studied included all cases of marked anemia, regardless of type, which were on the Stanford Medical Service of the San Francisco County Hospitals and those cases in private practice in which the treatment could be satisfactorily controlled. The total series consisted of 50 cases which were observed in a period of 8 months. In each instance, the patient was seen and studied clinically by one or both of us.

In all but 3 cases, two trained technicians made the blood examinations and the same technician always made all the examinations on the same individual. Hemoglobin estimations and red blood cell counts were done from one to three times a week throughout the period of study, the frequency of examination depending on the severity of the anemia and the availability of the patient. The hemoglobin examinations were made with the Sahli hemoglobinometer by choice, but at times the Tallqvist method was utilized. In 33 cases reticulocyte counts were made. In a few instances patients were not available for a sufficient number of counts to be of any value. If the red blood cell count was over 3 million, reticulocyte studies were not usually done. Counts were made two or three times a week for the first 2 weeks and frequently throughout the further course of treatment. A count was always made before the treatment was started. The intravital staining method of Wyckoff[6] was employed and proved satisfactory. As a rule only 200 cells were counted, as variations in reticulocyte per cent, which are less than one-half of 1 per cent are not considered significant. Where no reticulocytes were encountered after observing 200 cells, the count was recorded as less than one-half of 1 per cent, which corresponds to a normal figure. As Price-Jones[7] and others have empha-

sized the important relationship between red blood cell sizes and successful liver therapy in Addison-Biermer anemia, the average erythrocyte diameters were estimated two or three times a week for 3 weeks, and weekly thereafter. The estimations were made by means of Eve's Halometer as previously described by one of us.[8] White blood cell counts were carried out in several cases, but have not been included in this report.

The length of time patients should be treated was chosen as 3 weeks, because it was felt that any type of successful therapy would almost surely be demonstrated during this period. It was also felt that this was a sufficient time in which to demonstrate increases in reticulocytes and changes in cell size if such occurred. It is, of course, possible that a case of severe anemia might improve only after 3 weeks' treatment, but there is no good precedent that this is likely. The choice of dosage was a difficult problem, but it was decided to give 12 gm. daily, either in one dose or divided into 3 equal parts. This choice was based on the fact that this was the average dose recommended by the manufacturers of the extract, but it seemed quite likely that larger doses would prove to be efficacious in some cases. Two cases received only 8 gm. daily, while 1 case received 16 gm. daily for a part of the treatment. Two cases received 24 gm. daily. Certain patients were able to take the extract in water without difficulty but others could not. Consequently, the extract was frequently given in whatever vehicle it was best tolerated. Orange juice, grapefruit juice and hot peppermint water often proved satisfactory. No untoward effects on the stomach were noted.

The 50 cases studied have been divided into three groups on the following basis.

The first group is composed of 23 cases in which we felt that a definite disease was responsible for the production of the anemia. Table 1 shows a wide variety of disorders, which are generally accepted as causing secondary anemia. The second group is composed of 14 cases, all of which were secondary to hemorrhages. Most of these patients suffered from chronic hemorrhages, but in 4 the history suggested that the bleeding was acute (Table 2). Group III (Table 3), includes all cases in which no satisfactory reason for the anemia could be definitely determined. These 13 cases include several examples of what may be called "dietary anemia" and "toxic anemia," but such an etiology could only be suspected and could not actually be proved. Actually every effort was made to determine the clinical diagnosis on all of these 50 cases and it was surprising to find in how many instances it was impossible to come to any agreement as to the exact causative factor.

The tables show the clinical diagnosis, the degree of anemia before their treatment, and the exact length of treatment. For the three groups they also show in the majority of cases the degree of improvement at the end of a 3 weeks period as a basis of comparison. The date and degree of maximum reticulocyte response and the red blood cell size before and after treatment are also recorded. In the last column in each table is noted whether or not the patient improved and this is based upon the changes in the red blood cell count at the end of a 3 weeks period. These results have been arbitrarily divided into three classes and designated as marked improvement, moderate improvement, and no improvement at all.

TABLE 1.—THE RESULTS OF LIVER AND IRON THERAPY IN 23 CASES OF ANEMIA SECONDARY TO SOME SYSTEMIC DISEASE. (DOSE—12 GM. DAILY.)

Case No.	Diagnosis.	Before treatment.			Gain in 3 weeks.		Length of treatment, days.	End of treatment.			Day and degree of highest reticulocyte count.	Improvement.
		Hgb., %	R.B.C., millions, per c.mm.	Size, micra.	Hgb., %	R.B.C.		Hgb., %	R.B.C., millions, per c.mm.	Size, micra.		
25	Biliary fistula	55	3.9	7.7	..	...	15	60	3.1	7.6	....	None.
42	Lung abscess; sepsis	60	3.9	7.5	6	680,000	21	66	4.5	7.5	....	Moderate.
49	Cancer of esophagus	50	3.8	7.7	None	None	19	50	3.8	7.6	....	None.
3	Colon cancer; empyema	45	3.5	7.6	15	420,000	27	54	3.4	7.5	4th day—7%	None.
20	Cirrhosis of liver	68	3.5	7.7	None	None	21	58	2.6	7.7	....	None.
19	Pyelitis	50	3.4	..	No	record	39	65	4.0	..	....	Moderate.
36	Pulmonary tuberculosis and pneumokoniosis	60	3.2	7.6	5	None	18	55	3.2	7.6	<0.5%	None.
46	Colon cancer with hemorrhages during treatment	50	3.1	7.7	..	...	12	50	3.1	8.0	7th day—1%	None.
35	Cirrhosis and primary cancer of liver	62	3.1	8.0	None	670,000	24	62	3.7	7.7	<0.5%	Moderate.
32	Osteomyelitis	55	3.0	7.5	3	730,000	36	58	3.6	7.6	<0.5%	Moderate.
38	Pulmonary tuberculosis	63	2.8	7.7	4	570,000	20	67	3.4	7.3	14th day—1%	Moderate.
16	Sarcoma of humerus	52	2.6	7.6	None	None	25	50	2.0	7.3	<0.5%	None.
29	Pyelitis; sepsis	45	2.6	7.5	..	...	17	40	2.3	8.0	14th day—6%	None.
39	Cancer of ovary	55	2.6	7.6	5	220,000	21	60	2.8	7.5	11th day—1%	None.
37	Pulmonary tuberculosis	52	2.6	7.7	None	None	18	50	2.6	7.6	14th day—0.5%	None.
50	Cancer of stomach*	46	2.6	7.6	8	500,000	21	54	3.1	7.6	<0.5%	Moderate.
45	Pellagra, pulmonary tuberculosis; empyema	50	2.4	8.0	None	None	21	50	2.0	7.6	<0.5%	None.
44	Cancer of stomach	45	2.4	7.8	3	None	21	48	2.4	7.8	<0.5%	None.
28	Sepsis	55	2.3	7.6	1	550,000	36	58	3.5	7.5	6th day—2%	Moderate.
1	Chronic nephritis	30	2.2	7.3	2	200,000	28	32	2.3	7.3	7th day—5%	None.
48	Cancer of kidney	35	2.2	7.6	5	300,000	30	40	2.4	7.5	11th day—1.5%	None.
12	Lymphosarcoma, stomach	20	2.2	7.5	None	None	19	18	2.0	7.5	9th day—4%	None.
15	Hodgkin's disease	45	1.6	7.8	None	None	24	35	1.5	7.6	18th day—16%	None.

* Patient received 24 gm. daily.

Patient received 24 gm. daily.

TABLE 2.—THE RESULTS OF LIVER AND IRON THERAPY IN 14 CASES OF ANEMIA SECONDARY TO HEMORRHAGE. (DOSE—12 GM. DAILY.)

Case No.	Diagnosis.	Before treatment.			Gain in 3 weeks.		Length of treatment, days.	End of treatment.			Day and degree of highest reticulocyte count.	Improvement.
		Hgb., %	R.B.C., millions, per c.mm.	Size, micra.	Hgb., %	R.B.C.		Hgb., %	R.B.C., millions, per c.mm.	Size, micra.		
24	Menorrhagia	70	3.9	7.5	3	420,000	21	73	4.3	7.5	....	Moderate.
41	Abortion	68	3.9	7.5	2	450,000	25	70	4.3	7.5	....	Moderate.
26	Menorrhagia	68	3.6	7.5	2	320,000	21	70	4.0	7.5	....	Moderate.
47	Hemophilia	58	3.1	7.2	6	660,000	60	73	4.0*	7.3	....	Moderate.
17	Duodenal ulcer	48	2.6	7.6	..	...	11	33	2.0	7.8	10th day—2%	None; cont. bleeding.
18	Hemorrhagic colitis	35	2.4	8.5	5	490,000	59	70	3.8	..	13th day—8%	Moderate.
11	Hemorrhoids	26	2.1	8.0	29	1,000,000	50	70	4.2	7.6	18th day—6%	Marked.
43	Visceral purpura	35	2.1	8.0	..	...	16	62	3.4	7.6	....	Marked.
5	Duodenal ulcer*	35	2.1	7.9	15	1,120,000	57	66	4.5	7.5	17th day—8%	Marked.
30	Gastric hemorrhage; probable cirrhosis	40	2.0	8.3	10	830,000	31	52	3.1	7.8	4th day—6%	Moderate.
34	Acute hemorrhages from fibroid	24	1.9	8.2	33	2,220,000	21	57	4.2	7.6	9th day—8%	Marked
4	Chronic epistaxis†	20	1.5	8.4	17	1,660,000	60	65	4.4	8.0	....	Marked
8	Duodenal ulcer‡	30	1.5	8.2	20	1,670,000	21	50	3.2	8.0	....	Marked.
27	Gastric hemorrhage; ammonia poisoning	30	1.2	8.1	..	...	7	30	1.8	7.9	3d day—6%	? Marked.

* Patient received only 8 gm. daily.
† Patient received only 8 gm. daily.
‡ Patient received 16 gm. for the first 10 days of treatment.

TABLE 3.—THE RESULTS OF LIVER AND IRON THERAPY IN 13 CASES OF ANEMIA OF UNKNOWN CAUSE. (DOSE—12 GM. DAILY.)

Case No.	Diagnosis.	Before treatment.			Gain in 3 weeks.		Length of treatment, days.	End of treatment.			Day and degree of highest reticulocyte count.	Improvement.
		Hgb., %	R.B.C., millions, per c.mm.	Size, micra.	Hgb., %	R.B.C.		Hgb., %	R.B.C., millions, per c.mm.	Size, micra.		
6	Anemia, ? cause	65	4.2	7.3	8	741,000	23	73	5.0	7.3	....	Moderate.
40	Leg amputation; anemia, ? cause	60	3.8	7.8	7	430,000	20	67	4.3	7.5	14th day—1.9%	Moderate.
7	Morphin addict; undernutrition ?	50	3.5	7.6	None	None	25	48	3.8	7.5	25th day—3%	None.
33	Anemia, ? cause	75	3.4	7.4	None	460,000	36	81	4.7	7.4	....	Moderate.
2	Neuritis; anemia, ? cause	68	3.4	7.6	None	400,000	32	72	4.3	7.5	....	Moderate.
9	Tabes and As. therapy	34	3.3	7.7	8	270,000	21	42	3.5*	7.5	....	None.
13	Spastic paralysis; anemia, ? cause	65	3.2	7.9	..	...	10	78	4.0	..	....	? Marked.
21	Gonorrhea; ? dietary anemia	53	3.0	7.6	14	450,000	19	65	3.5	7.2	3d day—3%	Moderate.
31	Bulbar paralysis; ? dietary anemia	42	2.6	7.6	6	660,000	43	65	3.8	7.3	8th day—3%	Moderate.
22	Gastritis; ? dietary anemia	50	2.3	7.6	15	1,190,000	21	65	3.5	7.5	7th day—6%	Marked.
23	Anemia, ? cause*	45	2.1	8.0	13	840,000	24	60	3.0	7.7	<0.5%	Moderate.
10	Anemia, ? cause	18	1.6	8.5	14	490,000	44	42	2.8	8.5	9th day—3%	Moderate.
14	Lues and As. therapy	30	1.5	8.2	26	790,000	43	65	3.2	..	21st day—8%	Moderate.

* Patient received 24 gm. daily.

As in cases of Addison-Biermer anemia which respond well to liver therapy there is usually a gain of about 1 million or more red blood cells in the first 3 weeks of treatment, all the cases of secondary anemia which made this same striking increase are classed as marked improvement. Those cases which gained about 500,000 red blood cells and some hemoglobin are classed as moderate improvement, although it is quite certain that such gains might conceivably occur without any effect from the therapy. This is particularly true when the anemia follows acute hemorrhages. Nevertheless, when the red blood cell increase occurred corresponding to the liver extract therapy, it was felt justifiable to classify the response as attributable to the mode of treatment. Those cases which made no gain, or even lost, made up the group in which no improvement occurred. Under such a classification borderline cases were bound to occur, and in such instances these cases were included in the less favorable group. The changes in the red blood cell count were chosen as a more accurate indication of response than hemoglobin changes on the basis of similar work in Addison-Biermer anemia. In grouping the cases of anemia for comparison, account has not only been taken of the cause of the anemia, but also of the severity. Those cases in which the anemia was the mildest are listed first in the tables, and the more severe cases are listed in the order of their severity. It must be borne in mind that cases of moderate anemia cannot be expected to improve as strikingly as cases of severe anemia and this must be taken into consideration in comparing the cases in the three tables.

In reviewing the results of therapy in the group of cases included in Table 1 it is evident that anemia secondary to some general systemic condition does not respond well to treatment. Out of 23 cases, 16 showed no improvement whatsoever, and of the 7 cases which did improve, none showed marked improvement. In 10 instances various types of neoplasm were the obvious cause of the anemia, and all of these proved to be therapeutic failures, except Case 50 with a malignant ulcer of the stomach. As this patient gave a history of previous unsuccessful treatment on an average dose of secondary anemia liver extract and iron, we used double the dose, or 24 gm. daily, with remarkable clinical improvement, including a gain in weight and strength. This experience suggests that larger doses might have been more successful in the other 9 cases. When the anemia was caused by chronic infection, the outlook was somewhat better. There were 9 such cases, 4 of which were due to tuberculosis, uncomplicated by hemorrhage. In the nontuberculous group 4 out of 5 cases showed moderate improvement, while only 1 case of tuberculosis improved. Of 2 cases of cirrhosis of the liver the blood count improved in 1, in the other it did not. The patient in which improvement occurred, Case 35, subsequently came to autopsy and showed a small primary cancer of the liver. As he

presented all the usual clinical and autopsy findings of cirrhosis, and as the neoplasm was small, he was not included in the group in which malignant disease was held responsible for the anemia. A case of long-standing biliary fistula, and a case of chronic nephritis in which pronounced anemia was the chief feature for several months failed to improve. On the whole the treatment carried out in this group of anemias was unsatisfactory, except that improvement occurred in the patients with infections where the cause of the anemia might ultimately be overcome.

The results of the treatment recorded in Table 2 are in sharp contrast to those just reviewed. Here the anemia was the result of blood loss, and in all but one of the 14 cases improvement occurred, and in one-half the cases the red blood cell count increased so rapidly that the increase could be compared to that occurring in Addison-Biermer anemia after whole liver therapy. Case 17 which did not improve, continued to bleed extensively and has only been included in the series to emphasize that persistent profuse blood loss will negative the beneficial effects of the treatment. Actually the degree of improvement is even better than indicated in the table, for 3 of the 6 cases designated as moderate, had an initial red cell count of over 3,500,000 when a gain sufficient to be designated as marked could hardly be expected. In 2 further cases, 18 and 47, slight bleeding occurred during the treatment, so that they may not have received the maximum benefit from the liver extract and iron. Six of this group of cases, Nos. 4, 8, 18, 24, 26 and 34 had received iron therapy alone previous to coming under our observation, and without any material improvement being noted. In most instances the dosage was probably less than that given by us, although no accurate data is available. In summarizing this group it seems justifiable to state that the majority of these 14 cases of anemia secondary to hemorrhage were definitely benefited by the secondary anemia liver extract with iron.

It is difficult to interpret the findings in the miscellaneous group of cases recorded in Table 3. A comprehensive report would necessitate a detailed description of each individual case, which is beyond the scope of this paper, and would not disclose the exact cause of the anemia. Of the 13 cases included, 2 showed no definite changes in the blood count for the better, 9 showed moderate improvement during therapy, and 2 cases showed a really marked improvement. It seems probable that some of these cases might have improved moderately on no other treatment than bed rest and the hospital diet, but in other cases, such as 6, 10, 13, 14, 22, 23 and 31 it seemed probable that there was a causal relationship between treatment and improvement. The first of these 7 cases had received iron alone for 4 weeks without benefit. The dose was 12 grains daily. Cases 10 and 23 resembled Addison-Biermer anemia, and each received a course of treatment with Lilly's Liver Extract No. 343.

The blood counts did not improve until Lilly's Liver Extract No. 55 was given subsequently. The other 4 cases were in the hospital under observation from 2 to 4 weeks without improvement in the blood picture until they received specific anti-anemia treatment. Judging from the results obtained in this group of 13 cases it may be concluded that liver extract and iron may be of value in those anemias for which no cause can be found, and that they should be given a trial, if iron alone is unsuccessful.

It is very difficult to evaluate the efficacy of the treatment carried out in the whole series of 50 cases. It can be positively stated that 31 cases (62 per cent) improved coincident with the therapy, but it cannot be positively stated that in each instance the improvement was due to the therapy. Consequently the comparative figures for the three groups of cases shown in Table 4 must be taken guardedly. They may be summarized as follows: (1) posthemorrhagic anemias showed too great a uniformity of improvement to be disregarded: they were benefited; (2) anemias due to systemic disorders such as cancer, nephritis, chronic infections, etc., were not benefited as a group; (3) anemias of unknown etiology were not markedly benefited as a group, although in a few instances the liver and iron treatment seemed of value. Nevertheless, no results were obtained which might not have been obtained from iron alone.[9]

TABLE 4.—COMPARATIVE RESULTS OF LIVER AND IRON THERAPY IN 50 CASES OF SECONDARY ANEMIA.

Degree of improvement.	Group I. Anemia secondary to systemic disease, 23 cases.	Group II. Anemia secondary to hemorrhage, 14 cases.	Group III. Anemia cause unknown, 13 cases.	Totals.
Marked	0 = 0%	7 = 50.0%	2 = 15.4%	9 = 18%
Moderate	7 = 30.5%	6 = 43.6%	9 = 69.2%	22 = 44%
None	16 = 69.5%	1 = 6.4%	2 = 15.4%	19 = 38%

Reticulocyte counts in 33 cases (Table 5) showed results somewhat at variance with the generally accepted idea that a reticulocytosis is indicative of an improvement in the blood count in secondary anemias.[10] Of 24 cases showing an increase in the number of reticulocytes above the normal, 9 (more than a third), failed to show any increase in the red cell count or the hemoglobin per cent. The highest reticulocyte count encountered, 16 per cent in a case of Hodgkin's disease, was one of these 9 cases. We have seen reticulocyte counts up to 14 per cent in cases of untreated secondary anemia which did not improve. Such findings suggest that the reticulocyte, as an immature form of red cell, is indicative of bone marrow activity, but not necessarily successful activity as far as the anemia is concerned. Its appearance in numbers may not always be taken

as a precursor to betterment of the anemia. Table 5 also shows the average highest reticulocyte count to be 4.9 per cent, and the average day of the highest count to be the eleventh.

TABLE 5.—COMPARATIVE RESULTS OF RETICULOCYTE ESTIMATIONS.

Reticulocyte counts.	Group I. Anemia secondary to systemic disease, 23 cases.	Group II. Anemia secondary to hemorrhage, 14 cases.	Group III. Anemia cause unknown, 13 cases.	Totals.
Total cases	18	7	8	33
Cases showing increased counts	10	7	7	24
Cases improved, showing increased counts	2	7	6	15
Cases unimproved showing increased counts	8	0	1	9
Average per cent increase	4.5%	6.3%	4%	4.9%
Average day of highest count	10.1	10.6	14	11.3

TABLE 6.—THE EFFECT OF MACROCYTOSIS OF THE ERYTHROCYTES ON THE COURSE OF ANEMIA.

Cell-size estimations.	Group I. Anemia secondary to systemic disease, 23 cases.	Group II. Anemia secondary to hemorrhage, 14 cases.	Group III. Anemia cause unknown, 13 cases.	Totals.
Total cases	22	14	13	49
Cases showing initial macrocytosis	2	8	3	13
Cases improved showing initial macrocytosis	1	8	3	12
Cases unimproved showing initial macrocytosis	1	0	0	1

The average diameter of the erythrocytes was estimated in every case of the series but one. Table 6 presents a correlation between macrocytosis of the red corpuscles and the course of the anemia for each of the three groups of cases and for the total of 49 cases. It has been noted that in posthemorrhagic anemias there is a tendency toward macrocytosis of the red cells,[11] particularly if the anemia is pronounced. This is well shown in Tables 2 and 6 by the fact that over one-half the cases of this group showed an average red cell diameter of 8 μ or over in the dried film, which is above the normal.[8] In 13 cases of the whole series in which a macrocytosis was present before treatment, 12 showed improvement under therapy, and in 6 the improvement was marked. Eight of the cases successfully treated were in the group of anemias due to hemorrhage. The single patient whose blood did not improve was an old Japanese with a definite pellagra, advanced pulmonary

tuberculosis, and an empyema, who died 2 days after the liver and iron therapy was stopped.

It is evident that red cell macrocytosis indicated that liver and iron therapy would be successful in this small series of 13 cases. Eighteen other cases with erythrocytes of normal average diameter also improved, but in all but 2 of these the anemias were not sufficiently severe to have ordinarily been associated with macrocytosis. It seems then that in a study of a severe anemia the most important indication as to successful iron and liver therapy may be obtained from estimating the average mean diameter of the red cells, and that if this is above the average normal, the anemia is very likely to be benefited. This is comparable to the beneficial effects obtained in Addison-Biermer anemia by feeding liver, as the cases with a high average of large erythrocytes usually respond the best.

Conclusion. In a series of 50 cases of secondary anemia a secondary anemia liver extract combined with iron in a dosage of 12 gm. daily was followed by uniformly good results in all but 1 of 14 cases of posthemorrhagic anemia, while no marked improvement was obtained in 36 cases of anemia due to other causes, except in two instances in which the etiology was undetermined and might have been previous hemorrhage. The improvement in the group of anemias due to bleeding, the majority of which were chronic, seemed more pronounced than with other modes of therapy, and represented the same excellent hematopoietic response in human beings that Whipple produced in dogs on the same type of treatment.

Although 16 other cases of anemia improved moderately while taking the liver extract and iron treatment, some might have improved to the same degree without any treatment, and certainly others might have done as well on large doses of iron alone. A moderate increase in reticulocytes occurred in 24 cases, but as the red blood count increased in less than two-thirds of this number, their presence cannot necessarily be taken as a good prognostic sign. On the other hand, if a macrocytosis of the erythrocytes is present in a case of severe anemia a good response to liver and iron therapy may be expected.

If any conclusions can be drawn from this series of 50 cases, it seems justifiable to recommend the use of the combination of secondary anemia liver extract and iron primarily for anemias due to hemorrhage and for anemia of obscure etiology with macrocytosis of the red blood cells. It may also be of value in other secondary anemias, but at present there are insufficient data available to show whether it should take precedence over large doses of iron alone.

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A STUDY ON THE RESULTS OF 1500 BLOOD TRANSFUSIONS IN 1000 CASES.

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The current literature, too extensive to review here, is replete with reports of excellent results obtained by blood transfusion in various diseases. In fact, this mode of therapy seems to have become a panacea for all ailments. However, one who has performed a considerable number of transfusions, and has studied the results obtained, becomes somewhat skeptical about the universal value ascribed to this procedure. We have, therefore, analyzed the results obtained from 1500 blood transfusions performed on 1000 patients who were suffering from various diseases.

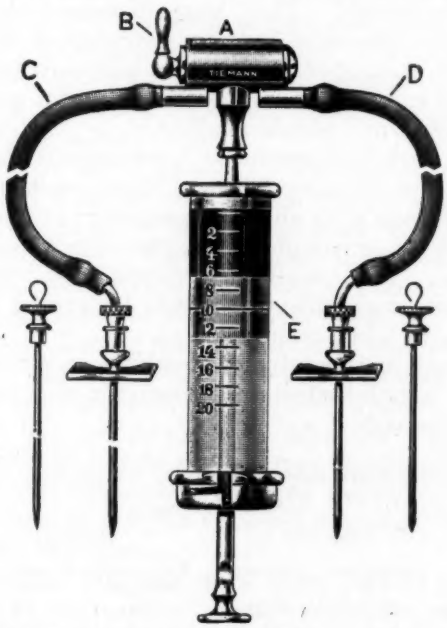
Technique. The group of the patient was determined and the patient's blood was cross-matched with the blood of an homologous donor preceding each transfusion, including repeated transfusions in the same case. Unmodified whole blood was transfused in every instance.

Lederer's* modified Miller apparatus (see illustration) was employed in all cases and was found to be simple and satisfactory. A 20-cc. Luer syringe was used in transfusions for adults and a 10-cc. Luer syringe for children. Normal saline was used to cleanse the syringes and apparatus to insure patency of the system. An 18-gauge Kaliski needle was used for adults and a 20-gauge for children. Hypodermic needles were occasionally employed in cases of small transfusions in very young infants in whom incision for a vein is extremely undesirable. For the donor a 15-gauge Kaliski needle was found most satisfactory. An ordinary muslin bandage, twice

* For a detailed description of the technique employed with this apparatus, the reader is referred to a paper by Dr. Lederer in the J. Surg., Gynec. and Obst., 1923, **37**, 221.

wound around the donor's arm supplied adequate constriction when properly adjusted.

The transfusion was, as a rule, performed in the patient's room, with the patient in bed instead of on an operating table, and the donor seated at the bedside. Since it is not necessary to fix the apparatus to any stationary object, the entire outfit was found to be less cumbersome than in most of the other methods described. As a result, the patient usually sensed the simplicity of the procedure, which helped to eliminate the psychic element of fear. In performing transfusions on children and irrational adults, however, it was found necessary to fix the patient's arm by strapping it to a projecting armpiece of a board especially constructed for this purpose, and placed beneath the patient. Such a support can be readily improvised. In these instances, of course, a nurse and an assistant are indispensable. In all other cases, however, one can perform the transfusion unassisted.



It was never found necessary to incise the donor's arm for a vein, and very rarely in adults or older children. Incision had to be resorted to in about 20 per cent of the cases of infants and very young children with collapsed and very small veins.

The dosage varied in each case, depending upon several factors, namely, the age of the patient, the degree of anemia, the cardiac, pulmonary and renal condition as well as the reaction of the patient during the transfusion. Infants and young children received from 50 to 200 cc. of blood, depending on the weight of the child, the general rule being about 20 cc. of blood per kilogram of body weight. Older children received about 150 to 300 cc., the exact amount being determined by the various factors mentioned above in each individual case. The average dose for adults was about 500 cc., although in some instances only 250 cc., while in others as much as 1000 cc. was given. The average time for the administration of 500 cc. of blood was about 20 minutes. In some cases of severe hemorrhage, however, about 1000 cc. were injected in less than 10 minutes in order to counteract rapid loss of blood.

We are cognizant of the fact that in the absence of controls it is frequently very difficult to determine when a blood transfusion is beneficial or not, because the criteria for estimating the value derived from any therapeutic procedure, such as a blood transfusion are not well defined. Thus, a patient may feel symptomatically better or worse following a transfusion and yet the changes noted may be due, not to the transfusion, but to other influences, legion in number. This is especially true in chronic diseases, where, regardless of the therapy employed, the patient is apt to be in a better condition at one time than at another.

On the other hand, there are instances when the part which blood transfusion plays in improving the condition of the patient can be better estimated. Thus, many diseases with severe anemia are known to be alleviated by administration of blood. In some instances, as in cases of pernicious anemia treated with liver, transfusion of blood is of definite aid in the treatment and may be considered of "adjuvant" beneficial effect.

Then again, the beneficial effect of transfusion is obvious in certain cases of persistent bleeding where a blood transfusion sometimes produces hemostasis after all other measures have failed. In occasional instances it is even a life-saving procedure by virtue of replacement of blood. Thus, in shock resulting from extensive hemorrhages, such as those due to trauma, impending death may be combated only by blood transfusion.

Reactions such as those due to blood incompatibility, etc., must be considered harmful effects of transfusion and sometimes, even contributory to death.

TABLE 1.—THERAPEUTIC EFFECT OF BLOOD TRANSFUSION IN 1000 CASES.

General Summary.

Group.	Beneficial.		Harmful.		
	Life-saving.	Adjuvant.	Unfavorable response.	Contributory to death.	Questionable.
Number of cases	14	232	28	9	717
Per cent	1.4	23.2	2.8	0.9*	71.7

* In some of these cases the patient was dying, and transfusion was merely a final heroic measure (see Table 4).

Discussion of General Results. Facts no less obvious than those mentioned above have guided the writers in classifying the results of the 1500 transfusions, as shown in Table 1. When there was any doubt as to whether the transfusion was beneficial or not the case was placed in the "questionable" group. From a study of Table 1, it is apparent that in 71.7 per cent of the cases blood transfusion yielded either questionable results or results which were neither beneficial nor harmful. This is in striking contrast to the results reported by the British Red Cross,[1] which in a study of 1215 transfusions found: Good or very good results in 57 per cent,

satisfactory results in 22 per cent, improvement followed by death in 14 per cent and no apparent result in 7 per cent.

In contrast to this, the high percentage of cases in the "questionable" group of the series here reported may be explained by the fact that the indications for the transfusion performed in many of these cases were not strictly medical. Thus, many of them were merely heroic measures to satisfy the family that everything possible had been done for the patient.

In 23.2 per cent of the cases the patients derived some benefit from the transfusions, although whatever improvement was noted could not be ascribed to the transfusion alone, hence they are designated in the table as of "adjuvant beneficial effect." In 2.8 per cent of the cases the patients reacted unfavorably to the transfusions with no subsequent improvement to compensate for the unfavorable reaction. In this group are included those who manifested untoward symptoms indicating disturbances in one or more of the following systems:

1. *Cardiovascular and Vasomotor.* The patient suddenly developed a rapid and irregular pulse, which became imperceptible and which was accompanied by marked dyspnea, orthopnea, cyanosis and extreme weakness. The vasomotor disturbances which frequently followed were evidenced by cold and clammy perspiration, marked pallor, sensation of hot flashes or chills.

2. *Respiratory.* During the transfusion or soon after the patient developed a dry, hacking cough, which at times was accompanied by pain in the chest and even hemoptysis. These symptoms sometimes persisted for a number of hours after the transfusion.

3. *Gastrointestinal.* Abdominal cramps rapidly followed by nausea and vomiting occasionally occurred during or following the transfusion. Occasionally, the vomiting was projectile in character and persisted for 48 hours.

4. *Genitourinary.* Suppression of urine varying in degree from moderate oliguria to complete anuria was another of the reactions encountered. Hematuria occurred rarely.

5. *Nervous.* Patients sometimes complained of severe headache, dizziness and a pounding sensation in the head for hours after the blood transfusion. More alarming reactions, however, were also encountered, consisting of syncope, convulsive seizures, stupor, nystagmus, transitory hemiplegia, or symptoms indicating cerebral hemorrhage or cerebral embolus.

An heterogeneous group of harmful effects may be added which consisted of the following: Thermic disturbances, *i. e.*, hyperpyrexia followed by chills; allergic reactions with or without urticarial skin eruptions; incompatibility reactions with all the phenomena of intravascular agglutination or hemolysis of blood; thrombophlebitis; aggravation of hemorrhagic tendencies in blood diseases, such as leukemia and thrombocytopenia; and last, but not least, the transmission of diseases, such as syphilis, malaria and others.

The causes of the reactions cannot be considered here. For a discussion of this subject, the reader is referred to a paper in press dealing specifically with this phase of the problem.[2]

TABLE 2.—CASES IN WHICH TRANSFUSION WAS A LIFE-SAVING MEASURE.

Case No.	Diagnosis.	Comment.
131	Lobular pneumonia	Female, aged 8 years. Condition grave. Temperature between 103° and 106°. Following exsanguination of 300 cc. of blood, 150 cc. transfused. Showed a strikingly rapid clinical improvement and temperature declined rapidly to normal.
295	Severe secondary anemia from excessive Roentgen ray and radium therapy	Male, aged 64 years, was helpless before each transfusion and within 24 hours after transfusion, returned to fairly active life. This man's life was prolonged by blood transfusions for a period of 3 years.
363	Lederer's anemia (acute hemolytic anemia)	Male, aged 3 years. Before transfusion, the anemia was rapidly progressive. The red cell count was 1,070,000 prior to, and 2,120,000 within 24 hours after transfusion, the number rapidly increasing to 4,020,000 within 12 days.
958	Lederer's anemia	Male, aged 16 months. Before transfusion he had only 900,000 red cells per c.mm. and appeared to be dying of anemia. A transfusion of only 120 cc. of blood had an immediate beneficial effect, after which the red cell count rapidly returned to normal.
177	Carcinoma of stomach	Male, aged 64 years. Lapsed into a state of shock from severe hematemesis of 1000 cc. of blood. Patient improved immediately after a blood transfusion of 500 cc.
986	Tonsillectomy, postoperative hemorrhage	Male, aged 25 years. Following a tonsillectomy, bleeding from the wound continued. No hemostatic measures proved effective and the patient was dying of hemorrhage. After a transfusion of 500 cc. of blood, the hemorrhage ceased almost at once.
164	Mastectomy for cystic degeneration of breast postoperative hemorrhage	Female, aged 39 years. Suddenly went into a state of shock from a postoperative hemorrhage. Improved immediately after a transfusion of 500 cc. of blood.
984	Amputation of toe, postoperative hemorrhage	Male, aged 22 years. Soon after amputation of toe, lost about a liter of blood from the wound, and lapsed into a state of shock. A transfusion of 600 cc. of blood relieved shock.
580	Hemorrhage following perineorrhaphy	Female, aged 38 years. Soon after operation she presented a picture of impending death due to shock from hemorrhage. She improved immediately after a transfusion of 500 cc. of blood.
870	Hemorrhage following perineorrhaphy	Female, aged 33 years. Shock from hemorrhage was immediately relieved after a transfusion of 500 cc. of blood.

Case No.	Diagnosis.	Comment.
640	Hemorrhage following oöphorectomy for large ovarian cyst	Female, aged 29 years. Shock from postoperative hemorrhage was immediately relieved after a blood transfusion of 750 cc.
810	Postpartum hemorrhage	Female, aged 25 years, with nephritic toxemia developed a severe postpartum hemorrhage and shock. A blood transfusion of 800 cc. immediately relieved the shock.
799	Placenta previa, postpartum hemorrhage	Female, aged 24 years. Shock from severe postpartum hemorrhage immediately relieved after a blood transfusion of 500 cc.
895	Ruptured ectopic, hemorrhage, shock	Female, aged 33 years. The rupture of the Fallopian tube was accompanied by a severe hemorrhage and shock which was relieved after a transfusion of 500 cc. of blood.

Discussion of the Cases in Which Transfusion Was a Life-saving Procedure. A study of Table 2 shows that the majority of cases in which transfusion was a life-saving procedure were those in which there was a rapid loss of a large volume of blood. Thus, in 9 out of the entire 14 cases the condition was one of shock from hemorrhage. The great value of blood transfusions in these cases is, of course, known to all and has been reiterated recently by numerous observers.[3–13] It is of significance to note that 6 of these 9 cases were either obstetrical or gynecologic complications. The inestimable value of blood transfusion in these complications has been emphasized in the recent literature.[14–18]

But the life-saving effect of transfusion apparently does not reside in the mere replacement of blood in all cases. Thus, in Case 131 it seems to have hastened the crisis in pneumonia and in Case 986 it proved to be the only effective hemostatic agent to combat what appeared to be fatal hemorrhage, after all other methods were found to be of no avail. Lindquist[19] reports an almost identical case of uncontrollable bleeding from the umbilical cord of an infant. Various hemostatic measures were tried for 6 days without avail. Then 25 cc. of mother's blood was injected into the longitudinal sinus and the bleeding stopped immediately.

The value of blood transfusion in the cases of Lederer's[20] anemia deserves special mention. Lederer's original observation, that transfusion acts almost as a specific in this disease, has been confirmed in his cases of this series, as well as in 5 subsequent ones which are not included in this study. Similar reports of the life-saving effect of blood transfusion in cases of Lederer's anemia have been reported by European writers.[21,22] The patient, usually a child, with evidences of a rapidly developing hemolytic anemia, which appears to be leading to a fatal termination, makes an uneventful recovery very quickly after a blood transfusion.

TABLE 3.—CASES BENEFITED BY TRANSFUSION.
(*Exclusive of Cases in Table 2*).

Group.	Diagnosis.	Cases transfused.	Cases benefited.	Per cent.
Hemorrhage	Hemophilia	6	5	83.3
	Thrombocytopenia	8	1	12.5
	Epistaxis	6	4	66.6
	Gastric and duodenal ulcer	38	17	44.7
	Ectopic gestation	13	5	37.6
Anemia	Pernicious anemia	29	13	44.8
	Secondary anemia	207	67	32.3
	Leukemia	32	9	28.1
Infection	Ulcerative colitis	12	8	66.6
	Mastoiditis	17	5	29.4
	Peritonitis	12	3	25.0
	Pneumonia (lobar and broncho)	108	25	23.1
	Subacute bacterial endocarditis	18	4	22.2
	Erysipelas	9	2	22.2
	Sepsis (miscellaneous)	207	31	10.1
Miscellaneous diseases	Shock of difficult labor	4	2	50.0
	Intestinal intoxication in children	35	17	48.5
	Surgical shock	44	12	27.2
	Uremia	9	2	22.2

Discussion of Definitely Benefited Cases. In Table 3 an attempt has been made to classify into disease groups those cases in which transfusion was definitely beneficial. (It does not include the cases mentioned in Table 1.) The total number that had received blood transfusions, the number of cases in which the transfusion proved to be definitely beneficial and the percentage of cases benefited are recorded for each disease. The conditions for which the greatest number of cases received transfusion were those of secondary anemia, sepsis, pneumonia, surgical shock, bleeding gastric or duodenal ulcers, intestinal intoxication in children, leukemia and pernicious anemia. The number of cases of other conditions studied in this series is too small from which to draw any definite conclusions as to the value of blood transfusion. For a rough estimate, however, the percentage benefited in these instances will also be found in Table 1.

It will be noted that the greatest percentages of cases in which transfusion proved to be of definite value were found in the following groups, in order of importance: Intestinal intoxication in infants, pernicious anemia, bleeding gastric or duodenal ulcer, including cases during massive bleeding; secondary anemias, due to miscellaneous causes; leukemia, surgical shock and pneumonia. In this study the percentage of cases of intestinal intoxication benefited by transfusion compare favorably with that found by Browne,[23] Robertson,[24] Sidbury,[25] Moore[26] and many other writers.

In the group of patients with pernicious anemia blood transfusion stimulated remissions and alleviated many of the unpleasant symp-

toms. In some of these instances, and also in cases of severe secondary anemia, transfusion may prolong life for years, as exemplified by Case 295 of Table 2.[27] Jones[28] and Yates[29] have reported similar cases. In some instances liver diet and iron or arsenic are insufficient to cause a remission unless supplemented by blood transfusion which stimulates the bone marrow, or which keeps the patient alive until there is a response to the liver therapy, as pointed out by Goodall,[30] Manson-Bahr[31] and Don.[32] There is absolutely no danger in transfusing patients with actively bleeding gastric or duodenal ulcers. In no instance of this series did the rise in blood pressure due to the transfusion renew active bleeding.[33] In reviewing the recent literature, one finds that the old fear of causing renewed bleeding or dislodging a thrombus in a vessel by transfusion of a large amount of blood is entirely unwarranted. Bernheim[34] found it safe to give about 400 cc. when the blood pressure reached 70 mm. Out of 121 cases of gastric and duodenal hemorrhage Keynes[35] obtained good results in 103 and no change in 18 cases. Johansson[36] obtained favorable results in 71 per cent of 28 cases of bleeding gastric ulcer. Similar observations were made by Hesse,[37] Rausche,[38] Plehn,[39] Bastedo[40] and others. Kordenat[41] found that an increase of blood pressure from 108 to 190 and from 130 to 230 mm. did not materially disturb a clot in a small branch of the femoral artery of a dog. In his cases of bleeding gastric ulcer transfusions of 750 cc. of blood stopped the hemorrhage in each instance.

In leukemia the beneficial effects were only transitory, the improvement undoubtedly being due to the improvement of the anemia. Septic conditions for which many have advocated blood transfusion as treatment *par excellence*[42–56] have been benefited but little and patients with bacteremia, not at all.

As for the value of transfusion in surgical shock, in the opinion of the writers, not enough blood was given in most cases of this series. This may account for the lower percentage of cases benefited as compared to the experiences of other observers.[5,7–13]

The percentage of cases of pneumonia in this series benefited by blood transfusion is small in comparison to that reported by other writers.[57,58,59] It is possible that the more favorable results found by others may be explained by a more careful selection of cases, as, for example, incipient pneumonias or those with mere congestive changes.

Discussion of Doubtful Cases. In Table 4 the effects in most of the cases cannot be satisfactorily correlated to the end results. Certain it is, however, that in none of them was death expected to occur as soon as it did. The least that can be said is that the transfusion may have been a contributing factor to the cause of the exodus in each of these cases. In Cases 683 and 796 the patients appeared to be in too poor a condition to withstand the strain of a

procedure even less disturbing than a blood transfusion. Cases 763 and 843 died of what appears to the writers to have been due to a condition of right heart overloading. Case 888 probably died of a cerebral embolus, the origin of which could not be determined. Case 606 died of a cerebral hemorrhage. This type of case deserves special emphasis. Individuals with aplastic anemias should be transfused with the greatest of caution because of the vulnerability of their vessel walls. Hemorrhages are prone to occur with the least amount of added strain to the vessels. Small transfusions given very slowly should be the rule in these cases.

TABLE 4.—CASES IN WHICH TRANSFUSION WAS CONTRIBUTORY TO DEATH.

Case No.	Diagnosis.	Age.	Comment.
608	Pneumonia	2½ mos.	Died a few minutes after transfusion of 70 cc. of blood.
642	Uremia	15 yrs.	Sudden unexpected death occurred 12 hours after transfusion. The patient's condition was made definitely worse by the transfusion of 350 cc. of blood.
665	Penumonia with empyema	6 yrs.	Immediately after transfusion of 150 cc. of blood, there was a sudden drop in temperature from 105° to 99°, accompanied by fatal shock.
683	Bleeding gastric ulcer	61 yrs.	The patient was in very poor condition and ceased to breathe during the transfusion.
763	Carcinoma of rectum	65 yrs.	Died during transfusion after having received 700 cc.
796	Leukemia (chronic myeloid)	48 yrs.	Died 10 minutes after a blood transfusion of 350 cc. The patient was not expected to die so suddenly.
843	Suppurative cholangitis, stone in common duct	36 yrs.	There was a rapid rise in temperature from 99° to 108° with associated signs and symptoms of cardiac dilatation.
888	Bronchopneumonia second degree burn	3 mos.	The clinical picture suggested an embolus causing sudden death after 80 cc. of blood were administered. The heart continued to beat for 20 minutes after cessation of respiration.
606	Aplastic anemia	24 yrs.	The patient received 750 cc. of blood. She soon developed cerebral complications indicating a cerebral hemorrhage and died very soon after.

Conclusions. 1. Of 1000 cases receiving a total of 1500 blood transfusions the results were either of doubtful benefit or of no effect whatever in 71.7 per cent.

2. Blood transfusion proved to be a life-saving procedure in 1.4 per cent of the cases. Most of these were patients who suffered a sudden loss of a large quantity of blood.

3. Some definite adjuvant beneficial effects were derived from transfusion in 23.3 per cent of the cases.

4. The reaction to the transfusion was unfavorable and the results harmful in 3.7 per cent of the cases.

5. The transfusion was apparently contributory to death in 0.9 per cent of the cases.

6. The excellent results from blood transfusion in the wide variety of diseases as reported by other writers could not be obtained in this investigation. Definitely beneficial results should be expected only in the type of case indicated in this study.

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DIFFERENTIAL ARTERIAL TENSION.

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The term differential pressure has been applied by Cyriax[1,2] to differences in readings of the arterial tension on the two sides of the body. Such asymmetry of the arterial tension may be of little clinical importance in some instances, whereas in other cases the asymmetry may be most significant.[3] Relatively little attention has been given to this interesting phenomenon. Extensive studies[4] of the difference in arterial tension in the arms as contrasted to the legs have revealed that the arteries in the leg bear pressures markedly higher than those in the arms; the pressure changes in a given limb which accompany a change of position may be largely accounted for by hydrostatic pressure changes.[4] Higher tension in the arms than in the legs is characteristic of coarctation of the aorta[3–5] An arteriovenous aneurysm in an extremity markedly lowers the arterial tension of that extremity.[6] The reputed significance of asymmetry of the arterial tension in pulmonary tuberculosis is very doubtful and probably invalid.[7]

Relatively meager data are available regarding the incidence of asymmetry of the arterial tension.[8] To determine this point the arterial tension was measured in both arms in a series of 600 individuals. The cases were derived from private patients, dispensary patients and applicants for life insurance. No children are included in the group, the ages ranging from 18 to 60 years. For purposes of definition and tabulation we have declared asymmetry to exist whenever the difference in systolic tension is 10 mm. Hg or greater or when the diastolic difference is 5 mm. Hg or greater. All deter-

minations were made with mercury manometers. Repeated readings on the right, left and again on the right were made in all instances of asymmetry to rule out errors due to fluctuation of the general tension from emotional or other causes. It is believed, therefore, that asymmetry under such conditions represents a significant pressure difference in the 2 arms. The results of these observations are best presented in tabular form:

TABLE 1.—SUMMARY OF BLOOD PRESSURE OBSERVATIONS ON 600 CASES.

	No. cases.	Per cent.	
Total number cases	600		
Males	415	69	
Females	185	31	
Cases with normal arterial tension	466	77	
Cases with high arterial tension	127	22	
Cases with low arterial tension	7	1	
Asymmetric cases	94	15.7	(% of total)
Asymmetric persistent in	75	80	(% of asymmetric cases)
Asymmetric males	69	74	
Asymmetric females	25	26	
Cases with normal arterial tension	59	60	
Cases with high arterial tension	34	35	
Cases with low arterial tension	6	5	
Systolic highest on right	18	19	
Systolic highest on left	11	12	
Diastolic highest on right	30	32	
Diastolic highest on left	18	19	
Both systolic and diastolic highest on right	18	19	
Both systolic and diastolic highest on left	4	5	
Systolic high right, diastolic on left	2	2.5	

The incidence of asymmetry in the present group of 600 individuals was slightly over 15 per cent. This is of similar magnitude to that reported by Kay and Gardner,[8] who found 20 per cent of asymmetry in a group of 125 patients. Bodenstab[9] reports far greater frequency in a short series, but his criteria of asymmetry included differences as low as 2 mm. In view of the normal physiologic fluctuation of the arterial tension,[10] such minor variations must be considered insignificant. It has long been assumed and taught that asymmetry of the arterial tension is most rare and unusual, being limited to a few cases of aortic aneurysm or trauma; such is clearly not the case.

Asymmetry does not appear more frequently in either sex. Asymmetry, however, is definitely more frequent in instances of hypertensive arterial disease than in those with arterial tension at normal levels. The instances of true hypotension were too few to warrant the drawing of conclusions.

There appears to be a slightly greater frequency of elevation of either the systolic or diastolic or both on the right side, but this is by no means marked. It has been noted in a number of instances, observed repeatedly, that when the arterial tension approached nor-

mal levels the asymmetry tended to diminish or disappear. This was true in both hypertensive and hypotensive patients. Systolic and diastolic asymmetry appear with almost equal frequency.

Physiologic explanation of the asymmetry was largely problematical in the majority of cases. Aortitis was observed three times, tabes twice. In a number of instances atheromatous patches at the orifice of the subclavian artery were suspected, although unproven.[3] The instance associated with cervical ribs was most instructive. In 3 persons injury to one arm with atrophy from disuse was associated with reduced tension upon that side, although curiously enough in other patients with injury to one arm asymmetry of the blood pressure was not elicited. A more detailed record of findings in several interesting instances of asymmetric arterial tension follows:

Case Abtracts. CASE 1.—Mr. P. R. S., aged 36 years, married, industrial chemist, was first seen, March 25, 1929, at which time he complained of pain in the region of the left occiput radiating downward to the shoulder. The pain was not affected by motion. The past history revealed an appendectomy in 1922, influenza in 1919 and tonsillitis once per winter. Recently hypertension had been discovered. Physical examination revealed 2 devitalized teeth, chronic pharyngitis, normal pulmonary fields, normal urine and a hemoglobin content of the blood of 74 per cent (Dare). The second aortic sound was accentuated, the cardiac apex was 1 cm. to the left of the midclavicular line. The arterial tension was 172/130 on the right and 145/100 on the left, falling to 130/80 on the right following the inhalation of amyl nitrite.[11] The family history revealed hypertensive disease in both parents. The following factors were considered as probably bearing upon the etiologic background of his hypertension: dental infection, hereditary influences, possible renal injury from benzine poisoning (occupation).

On April 3, 1929, the maximum specific gravity of his urine, after 14 to 16 hours' fluid deprivation[10,12] was 1.020. The arterial tension had fallen to 142/110 on the right under therapy with bismuth subnitrate.[10,13,14] Pain had disappeared.

On April 17 the arterial tension was 145/110; the maximum specific gravity had risen to 1.024 on repetition of the urinary concentration test.

On October 12 there occurred a sudden recurrence of pain in the left occipital region, radiating to the left shoulder and down the left arm. The reappearance of pain followed, carrying a heavy burden. The arterial tension was: right, 170/130; left, 130/80. Cervical rib was now strongly suspected. Roentgen plates revealed a left cervical rib. (Figs. 1 and 2.)

On October 19 the arterial tension was: right, 170/125; left, 140/102. Pain was much reduced.

On November 9 the tension was much more symmetrical: right, 142/105; left, 134/100; there was no pain. It was noted that the asymmetry of the arterial tension varied directly with the severity of the pain. Surgical intervention was urged because of the persistence of the compensatory hypertension on the side other than the lesion. It was felt that pressure from the cervical rib upon the brachial plexus depressed the arterial tension on the left side and that the systemic hypertension was at least largely compensatory. Spontaneous improvement was not to be anticipated, but exacerbation of the condition in the future was not unlikely. Gangrene of the hand is not uncommon as a result of pressure upon neural and vascu-

FIG. 1.—Case 1. Reduced Roentgen ray photograph showing the broad base of the cervical rib on the left side.

FIG. 2.—Case 1. Retouched reduced Roentgen ray photograph showing the extent of the cartilaginous tip of the cervical rib on the left side.

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lar structures by cervical ribs,[15,16] although in most instances cervical ribs are essentially asymptomatic.[17,18,19,20] Cervical ribs with large bases, such as this one, are frequently associated with elongated fibrocartilaginous tips which are not detected by Roentgen ray.[22] It has been stated[21,23] that the surgical indications depend directly on the degree of circulatory disturbance.

On November 23 the patient was operated upon by Dr. R. C. Bourland, of Rockford, Ill. The left cervical rib was found to be in close relationship to the brachial plexus which was wound about the long fibrocartilaginous tip. Pressure upon the plexus was obvious. Removal of the rib was most difficult but was successfully accomplished. Postoperative observations of the arterial tension revealed: November 23: right, 118/90; left, 98/74. November 24: right, 150/108; left, 130/100. November 25: right, 156/130; left, 140/110. November 26: right, 166/120; left, 160/110.

On January 11, 1930, the arterial tension was still somewhat asymmetric (right, 175/110; left, 140/100), although the diastolic asymmetry was much reduced. No arteriosclerosis was demonstrable, the hypertonia being purely spastic, as revealed by the response to the inhalation of amyl nitrite;[11] the blood pressure fell to 118/70. Bismuth subnitrate was again advised.

On March 5 the asymmetry had disappeared for the first time. The blood pressure was: right, 150/85; left, 142/86. Throughout the remainder of 1930 and to date in 1931 the readings revealed negligible or no asymmetry.

The above case is illustrative of more than the mere fact that a cervical rib may account for asymmetry of the arterial tension. In a major degree the vasotonic disturbance so engendered may be considered responsible for the patient's hypertension: Pressure on the plexus on the left depressed the tonus of the vessels of the left arm; in order to maintain an adequate circulation a compensatory hypertonia developed in the remainder of the circulation. This compensatory hypertension had persisted for a long but unknown time prior to its discovery. No immediate return to normal could be anticipated following the removal of the rib, for the prolonged hypertonia had undoubtedly created hypertrophy of the medial muscle of the arterioles and the earlier steps in the pathogenesis of hypertensive disease[10,14] had already occurred. The habit of arteriolar spasticity was present and the vicious circle of spasticity, arteriolar fatigue and hyperirritability was operative.[10] To overcome this "perpetuating factor" in hypertensive disease prolonged arteriolar relaxation and rest are necessary. It is in this connection that bismuth subnitrate has proven of value.[10,13,14] The above case is illustrative of the necessity for prolonged arteriolar sedation. The arterial tension has slowly returned to normal levels.

CASE 2.—Mrs. R. B., aged 45 years, Para-III. This patient had been under observation for 2 years with migraine and a menopausal type of arterial hypertension. The migraine had been successfully controlled by dietary régime, peptone injections, as suggested by Miller and Raulston,[24] and an increase in fluid intake. The arterial tension had been normal for 18 months. On June 27, 1928, the patient complained of pain in the right arm, extending from the wrist to the shoulder, which followed 24 hours after a period of numbness in the arm. Associated with this was a dull cephalalgia. Motion did not affect the pain; no tenderness could be elicited. There had been no recent infection. The nose and throat ap-

peared normal. The arterial tension was: right, 130/70; left, 128/80. The diagnostic impression at that time was neuritis, possible beginning herpes zoster.

No relief was obtained with the administrations of analgesics and acetylsalicylic acid. The distress continued unaltered to July 23, when the patient complained of marked soreness in the muscles of the right arm, with tremor resembling tetany. Roentgen ray of the shoulder revealed no abnormalities. On the advice of another physician a tonsillectomy was performed, November 2, by Dr. Crage, Chicago. One tonsil contained pus. No relief was obtained. On November 16 the patient first noted waves of erythemic redness and swelling of the right hand. Determination of the arterial tension at this time revealed marked asymmetry: right, 90/60; left, 130/70. No explanation of the asymmetry could be found. It was suggested that the patient take ephedrin sulphate, $\frac{1}{8}$ grain, three times per day, in an attempt at increasing the arterial tonus on the affected side. Within a few hours all discomfort ceased. She continued the ephedrin for several days and reported on November 24, at which time the degree of asymmetry of the arterial tension was much reduced: right, 118/70; left, 134/80. There has been no recurrence of pain since then, nor has any appreciable asymmetry been elicited.

In this second case we are at a loss to account for the asymmetry. It is quite certain no cervical ribs, aortic lesion or other gross abnormality existed. The prompt disappearance of the persistent pain upon therapy with the pressor substance ephedrin was most remarkable; it is probable that some ill-defined form of vasomotor palsy in the right arm was responsible for her symptoms.[28] After the first examination, in June, the arterial tension was determined only on the left (normal) side to avoid compression of the painful arm. Had bilateral studies been made sooner it is probable that much of the prolonged distress could have been avoided. It is notable that in both cases cited the subjective symptoms were limited to the side with the *lower* arterial tension.

Case 3.—Mr. W. E. G., aged 56 years, editor by occupation. On July 27, 1931, he first complained of paresthesia and numbness in the left hand and arm and some in the leg on arising in the morning. At times the numbness was associated with transient palsy of the left side. The paresthesia and palsy completely disappeared with activity. His past history was irrelevant to the present complaint. Examination revealed moderate pallor, the patient was tall and slender, of Stillar physique, the cardiac sounds were soft but clear and regular. The arterial tension was asymmetric: right, 118/88; left, 98/64. Urinalysis revealed normal findings. The hemoglobin was 90 per cent (Dare); erythroplastids, 4,520,000.

No thoracic or cerebral lesion could be found to account for the asymmetry. Roentgen ray examination failed to reveal a cervical rib. It was suggested he take $\frac{3}{4}$ grain ephedrin sulphate, once daily, on retiring. This resulted in distinct improvement of the morning numbness on the right side, but caused considerable insomnia. The arterial tension on July 30 was: right, 104/70; left, 102/70. The basal metabolic rate was found to be −25 per cent. Therapy with desiccated thyroid has since resulted in a gain in weight, complete cessation of the asymmetry of the arterial tension and disappearance of his distressing morning paresthesias.

It is characteristic of the symptoms attributable to either actual or relative hypotension[10] to be most notable early in the morning after sleep, at which time the arterial tension is lowest during the waking hours. This last case had a true hypothyroidism, with hypotension; the unexplained asymmetry exaggerated the hypotension on the left side sufficiently to produce subjective symptoms. Moderate hypotonia is usually asymptomatic. The primary mechanism creating the asymmetry is undetermined.

Asymmetry of the arterial tension has distinct clinical significance. It is far more frequent than is generally assumed. Failure to determine the arterial tension on both sides may result in gross diagnostic error, as illustrated in the second case cited. From the point of view of examination for life insurance, asymmetry is of importance, for grave errors are possible. A normal arterial tension on one side does not prove a normal tension on both. It is probable that the majority of instances of asymmetry are essentially transient, unless some definite organic lesion, such as aortitis, cervical rib, atrophy or trophic disturbance exists. But individuals in whom the vasomotor control is unstable are prone to reveal asymmetry of the arterial tension. Although the asymmetry may not be uniformly persistent, it tends to be recurrent. Both hypertonia and asymmetry may be attributed to variability of the vasomotor tone. Asymmetry of the arterial tension is more frequently encountered in patients with hypertensive disease than in those with normal blood pressure. Asymmetric reduction of the arterial tension in an extremity, as in the first case cited, may be a factor in the etiology of systemic hypertensive arterial disease by creating a prolonged compensatory arterial hypertonia. It is only the exceptional case which presents subjective symptoms.

Conclusions. Asymmetry of arterial tension, as defined in this paper, occurs in approximately 15.7 per cent of adults. It is more common in persons with elevated arterial tension and in those with vasomotor instability. Sex is not a factor. Elevation of the systolic and diastolic tension is somewhat more frequent on the right than on the left. Arteriolar spasticity, cervical rib, aortitis, injury to an extremity with atrophy, arteriovenous aneurysm and central trophic disturbances, as occur in tabes dorsalis, are all factors to be considered in evaluating the causation of persistent asymmetry.

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SOME RACIAL DIFFERENCES IN BLOOD PRESSURES AND MORBIDITY IN A GROUP OF WHITE AND COLORED WORKMEN.

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An experience of 11 years as an industrial physician in an industry employing 5074 men between the ages of 18 and 65, approximately one-third of whom were colored and the remainder white, showed some marked differences in physical characteristics and morbidity statistics in the two races. The most striking difference noted on physical examination was in the blood pressure. Accordingly a study was made of 28,221 blood pressure readings covering all of the ages represented in our personnel. There were approximately 14,000 individuals on whom readings were made, 8000 of whom were white and 6000 colored, or an average of two readings for each individual at different ages. Almost all of the whites were native born Americans. All the examinations were made on apparently healthy individuals and were noted on examinations of applicants for employment (9000) and annual health examinations (5000). None were included of individuals who were sick or who consulted us for medical advice. An average of three and four-fifths readings at different ages were made of the 5000 employees represented, or 19,000 readings, and a single reading of the 9000 applicants for employment. The period covered was from 1920 to 1930 inclusive.

Table 1 compares the average systolic and diastolic pressures of the white and colored men by age groups. The distribution into age groups is not equal, two-thirds of the readings having been made on men between the ages of 21 and 35. The numbers in the groups

from 41 to 65 years are too small for computing dependable averages, but are sufficient for comparative study. The average pressures in the group were systolic 124, diastolic 83. The average for the whites was systolic 121, diastolic 81; for the colored, systolic 128, diastolic 85. The average for the colored was therefore 7 mm. higher for the systolic readings, and 4 mm. higher for the diastolic than the average for the whites. This deviation occurred in each age group, the systolic pressure of the colored ranging from 4 to 13 mm. higher than the whites in the different age groups, and the diastolic pressures ranging from 2 to 6 mm. higher.

TABLE 1.—A COMPARISON OF BLOOD PRESSURES OF WHITE AND COLORED MALES BY AGE GROUPS.

Age groups.	Number of cases.			Average systolic pressure.				Average diastolic pressure.			
	White.	Col.	Total.	White.	Col.	*Difference.	Total.	White.	Col.	*Difference.	Total
18–20	1532	632	2164	117	125	8	119	77	81	4	78
21–25	4751	3680	8431	121	127	6	123	80	82	2	81
26–30	3462	2552	6014	120	126	6	123	80	84	4	83
31–35	2366	1984	4350	121	127	6	123	82	85	3	83
36–40	1550	1373	2923	122	128	6	125	83	87	4	85
41–45	905	644	1549	123	131	8	126	83	89	6	86
46–50	547	470	1017	126	137	11	131	88	92	4	90
51–55	334	405	739	130	134	4	132	90	93	3	92
56–60	250	430	680	126	139	13	134	90	96	6	94
61–65	156	198	354	139	148	9	144	92	96	4	94
Total	15853	12368	28221	121	128	7	124	81	85	4	83

* Millimeters of mercury that the average pressures of the colored men are greater than those of the white men.

Beyond 40 years of age the pressures of the colored men advanced more rapidly than that of the whites. The average systolic pressures of the whites between the ages of 18 and 40 was 120 and that of the colored was 127, a dominance of 7 mm. for the latter. In the group from 41 to 65 years the average was, for the whites 127 and for the colored 137, a dominance of 10 mm. for the latter, or 3 mm. more than in the 18 to 40 group. The diastolic pressures were for the 18 to 40 group, whites, 80; colored 84; difference 4 mm. For the 41 to 65 age group they were whites, 87; colored, 92; difference, 5. The dominance of the pressure of the colored was 1 mm. greater in the second age group than in the first.

Table 2 shows the maximum and minimum pressures in the series by age groups. The maximum pressures of the colored men are higher in practically every age group, and the average of the maximum pressures in all groups shows the colored systolic 17 mm. and the diastolic 4 mm. higher than that of the whites. The maximum systolic pressures in neither race is influenced by age, those of the younger ages being as high as those in the older groups. The highest recorded for a white man was at 24 years of age. The high

pressures in the younger ages were very probably influenced by a psychologic factor more than in the older men, and the pressures in the older men represent a greater amount of damage than in the younger. The average of the minimum pressures is the same in both races for the systolic, and for the diastolic that of the white men is 2 mm. higher than that of the colored. The minimum diastolic pressures for the colored however, cover a wider range than do those for the whites. The ranges are: white, 40 to 52; colored, 30 to 52. This may be accounted for by the fact that damage to the aortic valve and the first portion of the aorta is more common in the colored than in the whites, and occurs at an earlier age in the former race.

TABLE 2.—MAXIMUM AND MINIMUM BLOOD PRESSURES OF WHITE AND COLORED MALES BY AGE GROUPS.

Age groups.	Maximum.				Minimum.			
	Systolic.		Diastolic.		Systolic.		Diastolic.	
	White.	Col.	White.	Col.	White.	Col.	White.	Col.
18–20	180	190	110	128	78	84	40	46
21–25	224	220	138	160	74	80	38	32
26–30	200	210	130	132	74	72	40	30
31–35	210	226	140	142	70	60	50	40
36–40	200	240	140	160	78	80	40	38
41–45	218	224	140	150	80	80	40	42
46–50	200	260	162	148	60	64	42	32
51–55	210	242	164	160	94	96	40	52
56–60	204	204	140	142	96	90	50	50
61–65	200	200	162	150	88	80	52	52
Average	205	222	143	147	79	79	43	41

Table 3 shows the relation of albuminuria to blood pressures by races and age groups. While the percentage showing albumin in the urine is the same for both races, the age distribution and the difference in the two races of the relation of albumin to both the systolic and diastolic pressures is significant. From 18 to 30 years of age the whites show a preponderance of albuminuria, while in the ages 31 to 65 the colored are the most numerous. In the former age group 14 per cent of the whites and 12 per cent of the colored, and in the latter age group 9 per cent of the whites and 13 per cent of the colored had albumin in the urine. The lowest percentage for both races occurred in the ages 31 to 40. The average systolic pressure for the whites with albuminuria was 122, and without albumin was 121, a difference of only 1 mm. of mercury. In the colored group the figures were: with albumin 135, without albumin 128, a difference

TABLE 3.—RELATION OF ALBUMINURIA TO BLOOD PRESSURES OF WHITE AND COLORED MALES BY AGE GROUPS.

Age groups.	Number of cases.				Per cent with albumin.		Average systolic pressure.						Average diastolic pressure.					
	With albumin.		Without albumin.				With albumin.			Without albumin.			With albumin.			Without albumin.		
	White.	Col.	White.	Col.	White.	Col.	White.	Col.	Total.	White.	Col.	Total.	White.	Col.	Total.	White.	Col.	Total.
18–20	311	100	1221	532	20	16	117	127	120	117	124	119	76	82	78	77	80	78
21–25	682	457	4069	3223	14	12	121	129	120	121	126	123	80	84	82	80	82	81
26–30	392	252	3070	2300	11	10	119	131	124	120	126	123	80	87	83	80	83	81
31–35	167	176	2199	1808	7	9	123	132	128	120	126	123	87	85	86	81	84	83
36–40	106	129	1444	1244	7	9	126	138	133	122	127	124	86	93	90	83	86	84
41–45	65	76	840	568	7	12	126	143	135	123	130	125	88	98	93	81	88	85
46–50	49	89	498	381	10	19	130	150	143	125	133	129	96	100	98	87	90	88
51–55	57	87	277	318	17	21	135	145	141	129	131	130	95	99	98	90	91	90
56–60	52	88	198	342	21	20	132	146	141	124	137	132	94	98	96	89	95	93
61–65	26	46	130	152	17	23	140	152	148	139	146	143	89	97	94	92	96	94
Total	1907	1500	13946	10868	12	12	122	135	128	121	128	124	82	89	85	80	85	83

of 7 mm. The diastolic pressures showed the same trend and were as follows:

	Mm.		Mm.
White with albumin . . .	82	Colored with albumin . . .	89
White without albumin . .	80	Colored without albumin . .	85
Difference	2	Difference	4

The age distribution and the contrast in the difference between the pressures with and without albuminuria indicate that a larger proportion of the albuminuria in the whites was functional, especially in the younger ages, than in the colored, and conversely that the albuminuria in the colored represented a greater amount of kidney damage than in the whites.

In the same group, complete and reasonably accurate records were kept of the time lost over a period of seven years. Table 4 shows the actual number of cases of sickness, the actual number of days lost and the average duration per case, classified by races and by causes, using the nomenclature of the International Classification of causes of death. Table 5 further analyzes these figures, showing the annual rate per thousand, the average number of days lost per year by each individual, and the percentage of time lost by each disease group as compared with the total, classified in the same manner as in Table 4. In practically all of the cases of illness except malaria, the patients were treated by their own physicians. But all cases were supervised by our medical staff and represent in the main, actual disability and accurate diagnoses.

It is first noted that of the total number of 22,461 cases, 7666 or slightly more than one-third are colored. This is the approximate proportion of colored to white individuals in the group, as is indicated in the case rate of 623 per 1000 for the whites and 651 per 1000 for the colored, the case rate for the group being 632 per 1000. But when we note the average number of days lost per year by each individual, we find a greater difference in the two races. The whites lost an average of 8.05 days per year and the colored 9.79, the average for the group amounting to 8.62 days. The increased amount of time lost by the colored over the whites is due to the longer duration per case of illness of the colored (15 days), than of the whites (12.9 days). The average duration for the group is 13.6 days per case.

The analysis of the causes of disability reveal further racial differences. In the respiratory group, the frequency for the whites is greater, 260 per 1000, as against 194 per 1000 for the colored. The duration per case is, however, greater for the colored, 12.7 days per case as compared with 9.2 days for the whites, resulting in a greater amount of time lost per individual by the colored than by the whites (2.45 days per year by the colored and 2.39 by the whites). Nevertheless, the amount of time lost from these diseases as compared with the total time lost from all causes, is greater for

the whites than for the colored (whites 29.7 per cent and colored 25.1 per cent). Twenty-eight per cent of the time lost by the total personnel was due to the respiratory diseases.

TABLE 4.—NUMBER OF CASES OF SICKNESS DISABILITY, NUMBER OF DAYS LOST AND AVERAGE DURATION PER CASE, CLASSIFIED BY CAUSES IN A GROUP OF 5074 WORKMEN DURING A PERIOD OF 7 YEARS.

Name of diseases.	Number of cases.			Number of days lost.			Average duration per case in days.		
	White.	Col.	Total.	White.	Col.	Total.	White.	Col.	Total.
Influenza (11) . .	3963	1610	5573	38113	21069	59182	9.6	13.1	10.6
Tonsillitis and pharyngitis (109)	771	173	944	7209	1928	9137	9.3	11.1	9.7
Other respiratory diseases (97–107)	1432	500	1932	11447	5940	17387	8.0	11.9	9.0
Total respiratory diseases	6166	2283	8449	56769	28937	85706	9.2	12.7	10.1
Appendicitis (117) .	367	37	404	12657	1039	13696	34.5	28.1	33.9
Ulcer of stomach and duodenum (111 a–b) . . .	80	6	86	3935	488	4423	49.2	81.3	51.4
Other gastrointestinal diseases (112–116, 119–127) .	1734	783	2517	12238	5946	18184	7.1	7.6	7.2
Total gastrointestinal diseases . .	2181	826	3007	28830	7473	36303	13.2	9.0	12.1
Malaria (5) . . .	1466	1678	3144	16862	21639	38501	11.5	12.9	12.2
Tuberculosis pulmonary (31) . .	46	20	66	11168	3548	14716	242.8	177.4	223.0
Contagious diseases (1–4, 6–10, 12–30)	296	121	417	4327	2135	6462	14.6	17.6	15.5
Venereal diseases (38–40) . . .	217	285	502	5115	8097	13212	23.6	28.4	26.3
Infections (41) . .	259	86	345	2848	1605	4453	11.0	18.7	12.9
Hernia (118 a) . . .	87	42	129	4046	2226	6272	46.5	53.0	48.6
Genitourinary diseases, nonspecific (130–142) . .	327	142	469	7034	4318	11352	21.5	30.4	24.2
Diseases of skin, boils, etc. (151–154)	554	224	778	5082	3057	8139	9.1	13.6	10.5
Home injuries (non-industrial) (165–203) . . .	710	461	1171	11101	6518	17619	15.6	14.1	15.0
Rheumatism, neuralgia, arthritis, myositis, etc. (32, 82, 156, 158) . .	806	535	1341	11764	7481	19245	14.6	13.9	14.4
Chronic heart and kidney diseases (87–91, 129) . .	79	82	161	3596	6816	10412	45.5	83.1	64.7
All other diseases .	1601	881	2482	22469	11433	33902	14.0	13.0	13.7
Total . . .	14795	7666	22461	191011	115283	306294	12.9	15.0	13.6

This difference in the races is noted in all classes of respiratory diseases, but is most marked in cases of tonsillitis and pharyngitis. These two diseases are not listed with the respiratory diseases in the International Classification, but are included with them in our study. The annual rates are, for whites, 33 per 1000 and for colored 15 per 1000, less than half in the latter group of the number in the former. The time lost per case is greater for the colored, but the time lost

per individual per year is .30 day for the whites and .16 for the colored, or slightly more than half as much by the colored as by the whites.

TABLE 5.—ANNUAL RATES OF SICKNESS DISABILITY, AVERAGE NUMBER OF DAYS LOST PER INDIVIDUAL PER YEAR, AND PERCENTAGE OF TIME LOST IN EACH DISEASE GROUP, IN A GROUP OF 5074 WORKMEN DURING A PERIOD OF 7 YEARS.

Name of diseases.	Annual rates per 1000.			Days lost per individual per year.			Per cent of total time lost.		
	White.	Col.	Total.	White.	Col.	Total.	White.	Col.	Total.
Influenza (11) . .	167	136	157	1.61	1.79	1.64	20.0	18.3	19.3
Tonsillitis and pharyngitis (109)	33	15	27	.30	.16	.26	3.8	1.7	3.0
Other respiratory diseases (97–107)	60	43	54	.48	.50	.49	6.0	5.2	5.7
Total respiratory diseases . . .	260	194	238	2.39	2.45	2.40	29.7	25.1	28.0
Appendicitis (117) .	16	3	11	.53	.09	.38	6.6	.9	4.5
Ulcer of stomach and duodenum (111 a–b) . . .	3	5	2	.17	.04	.13	2.1	.4	1.4
Other gastrointestinal diseases (112–116–119–127)	73	66	71	.52	.50	.51	6.4	5.2	5.9
Total gastrointestinal diseases .	92	70	85	1.22	.63	1.02	15.1	6.5	11.9
Malaria (5) . . .	62	142	89	.71	1.84	1.08	8.8	18.8	12.6
Tuberculosis pulmonary (31) . .	2	2	2	.47	.30	.41	5.8	3.1	4.8
Contagious diseases (1–4, 6–10, 12–30)	12	10	12	.18	.18	18	2.3	1.9	2.1
Venereal diseases (38–40) . . .	9	24	14	.22	.69	.37	2.7	7.0	4.3
Infections (41) . .	11	7	10	.12	.14	.12	1.5	1.4	1.5
Hernia (118 a) . . .	4	4	4	.17	.19	.18	2.1	1.9	2.0
Genitourinary diseases, nonspecific (130–142) . .	14	12	13	.30	.37	.32	3.7	3.7	3.7
Diseases of skin, boils, etc. (151–154)	23	19	22	.21	.26	.23	2.7	2.7	2.7
Home injuries (non-industrial) (165–203)	30	39	33	.47	.55	.50	5.8	5.7	5.8
Rheumatism, neuralgia, arthritis, myositis, etc. (52, 82, 156, 158) . .	34	45	36	.50	.64	.54	6.2	6.5	6.3
Chronic heart and kidney diseases 87–91, 129) . .	3	7	5	.15	.58	.29	1.9	5.9	3.4
All other diseases .	67	75	70	.95	.97	.96	11.8	9.9	11.0
Total . . .	623	651	632	8.05	9.79	8.62	100	100	100

In the group of gastrointestinal diseases the effect of race on morbidity is still further demonstrated. In this classification the annual rate for whites, 92, the duration per case 13.2, the days lost per individual per year, 1.22, and the percentage of time lost compared with the total time lost, 15.1 per cent, are all greater than for the colored which are: annual rate 70, duration 9 days, days lost per year .63, and percentage of total time lost 6.5. There were five

times as many cases of appendicitis per 1000 in white employees as in colored. Only a few of the 37 colored cases went to operation, and the accuracy of the diagnosis in other cases may be questioned, while nearly all of the 367 white men were operated upon. There were only 6 cases of gastric or duodenal ulcer in the colored group, and none of these were confirmed by radiographic examination. In the majority of the 80 white cases the diagnosis was sustained by radiography.

In the group of malaria cases, the picture is reversed. Here the colored employees predominate in frequency, which is more than double that of the whites, duration per case, days lost per individual per year (2½ times that of the whites), and percentage of time lost which is double that of the whites. Significant is the high percentage of time lost by the colored, 18.8 per cent of the total, bringing the percentage of time lost for the whole group up to 12.6 per cent from this preventable disease. The diagnoses in half of the cases of malaria were confirmed by microscope. The predominance of malaria in the colored group is probably due more to their increased exposure than to a racial susceptibility. As a rule the white employees live in screened houses, while the homes of most of the colored men are not screened.

Pulmonary tuberculosis shows identical rates for white and colored, but the whites show a longer duration per case and consequently a greater amount of time lost. The increased duration of the white cases was due to the fact that the mortality rate was much lower than that of the colored and they consequently had a much longer absence during convalescence. The relative frequency in our group does not correspond to that noted in the general population where the colored race shows a much higher frequency than the white.

Contagious diseases were slightly more prevalent in the white personnel than in the colored.

The picture presented in the gastrointestinal disease group is further exaggerated in the venereal diseases. The frequency in the colored men is almost three times that in the white and the days lost per individual more than three times that of the whites. These figures are not, of course, a true census of venereal diseases in the group, but represent only the cases discovered and losing time.

The whites showed a greater number of local infections, skin diseases and cases of furunculosis, than the colored.

The frequency of hernias is identical in both races, but the duration of disability is greater for the colored.

Home injuries are more frequent among the colored, but apparently less severe than among the whites. This conclusion is modified as in the tuberculosis cases by the fact that the mortality rate, which is not shown in this study, is higher for the colored than for the whites.

In the degenerative diseases of the heart and kidneys we again find a marked predominance in the colored race. The case rate is more than double and the disability rate more than three times those of the whites. Five and nine-tenths per cent of the time lost by the colored was from these diseases and only 1.9 per cent of the time lost by the whites.

The *conclusions* drawn from this study are that in this group of white and colored males:

1. The blood pressures of the colored are higher than those of the whites.
2. The pressures after 40 years of age advanced more rapidly in the colored race than in the white.
3. Damage to the aortic valve occurs earlier and more frequently in the colored than in the whites.
4. Albuminuria is more often functional in the white persons, and more often indicative of nephritis in the colored.
5. The frequency of illness is the same in both races.
6. The recuperative powers of the colored are less than those of the whites.
7. The whites are more susceptible to respiratory and other infections, to gastrointestinal diseases, especially appendicitis and gastric and duodenal ulcers, and to skin diseases, than the colored.
8. The colored men are more susceptible to rheumatic and degenerative diseases than the whites.
9. Venereal diseases and malaria are more prevalent among the colored probably because of greater exposure and less prophylaxis.

STUDIES IN ATHEROSCLEROSIS.

I. Conditions in Childhood Which Predispose to the Early Development of Arteriosclerosis.*

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Whenever the complexities of a subject under investigation become so baffling that further progress seems impossible it is advisable to return to the simplest manifestations of the processes in question, and there seek out a new method of attack. That is what we have tried to do in relation to the centuries-old question of arteriosclerosis in studying its occurrence in young individuals.

* Read, in part, before the Annual Meeting of the Central States Pediatric Society, Cincinnati, Ohio, October 16, 1931.

From January 1, 1925, to January 1, 1931, there were 3072 autopsies performed on patients dying in the Cincinnati General Hospital. Of this number 1070 were under 30 years of age. These form the basis for this investigation. The material available for study consisted of the following: (1) Microscopic sections, averaging between 15 and 20 slides on each case, and including sections from all the principle viscera; (2) additional gross Zenker material and in many cases entire organs preserved in formalin or Kaiserling solution; (3) clinical and pathologic reports, the latter including both gross and microscopic findings.

The lesion dealt with in this investigation is the so-called simple arteriosclerosis, which begins as a degenerative process in the intima. In the early stages it is characterized by lipoid infiltration, in the later stages by fibrous tissue proliferation and calcification. There may also be ulceration and thrombosis, particularly when the process occurs in large vessels. When arterioles are affected they are likely to become occluded during the early stages of the process and the later changes may never occur. This report is not concerned with vascular changes of inflammatory origin as seen in syphilis, rheumatic fever and pyogenic infections. Periarteritis nodosa and thromboangiitis obliterans are also excluded.

A review of the pathologic material in these 1070 cases under 30 years of age revealed definite atherosclerosis of the aorta, arteries or arterioles in 79 cases. This figure does not represent the true incidence of atherosclerosis in this series. In many cases there was no formalin material available for fat stains. In such instances if the atheromatous change was so slight as to be questionable without special stains the case was not included.

The age distribution was found to be as in Table 1:

TABLE 1.—AGE DISTRIBUTION.

Age, years.	Total number studied.	Definite atherosclerosis.		Chronic renal lesions.	Rheumatic heart disease.	Diabetes.	Tuberculosis.
		No.	%				
Under 1	476	7	1.5	5			
1 to 5	154	2	1.3	2			
6 to 11	56	4	7.1	2	1	...	1
12 to 21	148	18	12.2	8	10	1	
22 to 29	236	48	16.1	27	12	3	4
	1070	79	7.4	44	23	4	5

It might be hoped that the 9 cases under 6 years of age would furnish very valuable data, in that they would present fewest complicating factors. However, all of these were found to be of unusual

complexity. Not one of them presented a simple diagnostic problem. A brief résumé of each case follows:

N–29–656, a stillborn, premature, breech-presentation, forceps delivery from a septic mother who died 13 days postpartum with acute pelvic peritonitis, bilateral salpingitis and septic lesions in other viscera. The baby had petechial hemorrhages in the viscera and, in addition, chronic foci of scarring and active inflammation in the kidneys. There was slight thickening of the renal arterioles and an area of definite atherosclerosis in the pulmonary truncus arteriosus. The latter lesion was so marked that there was actual narrowing of the lumen at that point. In addition, some of the pulmonary arterioles were thickened, apparently by intimal proliferation.

N–30–119, a stillborn, almost full-term delivery following premature separation of the placenta with bleeding. Delivery was followed by the passage of a large, fresh blood clot. The placenta was covered with much older clot. The fetal heart was definitely heard a few hours before delivery, but the child was born dead. There were a few definite atheromatous plaques in the pulmonary and coronary arteries, those in the former vessels being macroscopically visible. The lungs were edematous and atelectatic. There were a few petechial hemorrhages in the brain. The only other important findings were foci of lymphocytic infiltration and cellular degeneration in the kidneys and in the suprarenal medullæ.

N–30–416, an infant, aged 6 months, dying after a severe attack of diarrhea and bilateral otitis media in the late stages of which there was marked acidosis and urea retention. (Blood urea nitrogen, 105 mg.) The only pathologic changes in the kidneys were marked toxic swelling with extensive lipoid deposition in the tubules. Lipoids were also found in the thickened aortic intima and in the splenic arterioles. The splenic follicles were markedly hypoplastic and there was chronic inflammation in the pulp. The other findings were: Resolving lobular pneumonia, acute ulcerative esophagitis, subacute enterocolitis, early rickets and a terminal pulmonary embolus of undetermined origin.

N–29–356, a baby, aged 4 months, dying a few minutes after admission. No history was obtained. Autopsy findings: Chronic diffuse glomerulonephritis with marked renal arteriolar sclerosis; slight arteriolar sclerosis in the spleen, pancreas and liver; confluent lobular pneumonia; marked fatty infiltration in the liver; chronic periductile inflammation in the pancreas.

N–29–261, an infant, aged 10 months, developing convulsions in the terminal stage of bilateral otitis media. At autopsy petechial hemorrhages were found in the edematous brain and there were toxic changes in the viscera. The right kidney presented a moderate degree of hydronephrosis caused by what was apparently a congenital constriction in the right ureter. In this kidney there were wedge-shaped areas beneath the capsule which microscopically resembled very closely arteriolar nephrosclerosis. The vessels elsewhere in the kidneys and in the other viscera were not remarkable.

N–27–318, an infant, aged 9 months, dying with enteritis; no history was obtained. Autopsy findings: Chronic enteritis, generalized lymphoid hyperplasia, focal lymphocytic infiltration in suprarenal medullæ, definite atheromatous thickening of aortic intima.

N–26–156, an infant, aged 3 months, dying with otitis media complicating whooping cough. There was subacute peribronchitis, follicular necrosis in the spleen, fatty infiltration in the liver and several definite atheromatous plaques in the aorta. The splenic arterioles had narrowed lumina apparently caused by endothelial proliferation over hyalin masses in their walls.

N–28–413, a very complicated case, aged 5 years, having numerous congenital abnormalities and many acquired defects. Child had received very poor care and had been sick since birth. The most important conditions found at autopsy were: Marked emaciation, hydrocephalus, bilateral cataracts, secondary anemia, jaundice, ascites, phimosis, pyelitis, all stages of focal nephritis, rickets, dental caries, abscesses in the scalp and gastroenteritis. There was arteriolar sclerosis in the kidneys, spleen, liver and thyroid. Unfortunately no section of aorta was saved.

N–28–237, an infant, aged 17 months, dying with lobular pneumonia complicating whooping cough. The white cell count before death reached 170,000, with 80 per cent lymphocytes. There was marked hypoplasia of the Malpighian corpuscles in the spleen and the central arterioles had thickened walls. There was subacute and chronic focal glomerulonephritis with early renal arteriolar sclerosis. Many of the renal tubules were loaded with lipoids. Other findings were: Rickets, nodular proliferation of glandular tissue in suprarenal medullæ, increase in colloid in the thyroid, fine diffuse fatty infiltration in the liver.

Although these 9 cases revealed a great variety of pathologic lesions, there were a few points of similarity: (1) Seven of the 9 presented lesions in the kidneys; the only one of these cases in which the blood urea nitrogen was recorded showed marked urea retention. (2) Eight of the 9 presented chronic lesions somewhere in the body, some of which were certainly present before birth. (3) The only other findings which occurred with greater frequency in these cases than in the large group without arteriosclerosis were hypoplasia of the splenic corpuscles and lesions in the suprarenal medullæ.

In the next age group, 6 to 11 years, inclusive, only 4 of the 56 cases studied presented definite atherosclerotic lesions.

N–28–286, a child, aged about 9 years, had extensive suppurative pyelonephritis with marked intimal sclerosis of the medium-sized renal arteries and arterioles. The other findings were: Marked fatty invasion of the parathyroids, chronic splenitis, subacute and chronic laryngitis, fibrosis of the thyroid and pulmonary edema.

N–29–577, a child, aged 7 years; was very complicated. The findings were as follows: Hypoplasia of the cerebral arteries with massive cerebral hemorrhage; sickle-cell anemia; generalized lymphoid hyperplasia; hyperplastic bone marrow; acute bronchitis; multiple adenomatous nodules in the suprarenals; extensive chronic focal nephritis; atherosclerosis in the larger splenic arteries and the aorta; arteriolar sclerosis in the spleen, kidney and appendix.

N–29–297, a child, aged 7 years, had advanced pulmonary tuberculosis with caseation, cavitation, emphysema and extensive fibrosis. The process had extended through some of the vessel walls and lipoids were found in the thickened intima. There was focal lymphocytic infiltration in the suprarenal medullæ. The kidneys were not remarkable except for toxic changes.

The fourth case in this age group was a child, aged 10 years, dying with rheumatic pancarditis in which there was moderate atherosclerosis of the pulmonary arteries. No section of aorta was saved.

Of the 18 cases with atherosclerosis dying between the ages of 12 and 21 years, inclusive, 10 had rheumatic heart disease. The

vessels affected in these cases were particularly the pulmonary and coronary arteries and the first portion of the aorta. In the cases without atherosclerosis dying within this age period there was only 1 case of rheumatic heart disease and this one died with lobar pneumonia within 2 months of the onset of the rheumatic disease.

The remaining 8 cases in this age group all had chronic renal lesions. Two died of far-advanced arteriolar nephrosclerosis accompanied by generalized small vessel sclerosis. Six others presented chronic renal lesions of less severe degree, death having been the result of other causes. One of these died in diabetic coma at the age of 17 years and presented large atheromatous plaques in the aorta. Splenic follicular hypoplasia and suprarenal lesions occurred in 2 cases each. No other lesion occurred with any notable degree of frequency.

The last age group to be considered consisted of 48 cases dying between the ages of 22 and 29 years, inclusive. Although these were not "pediatric" cases at the time of death, many of the lesions showed evidence of origin in childhood, and this fact was often verified by the clinical history.

Here again we find rheumatic heart disease and chronic renal disease occurring with striking frequency. Twelve (25 per cent) of the 48 atherosclerotic cases had rheumatic heart disease. Only 1 of the nonatherosclerotic cases had rheumatic heart disease. This was a woman, aged 28 years, who died following a septic abortion, with vegetative endocarditis superimposed upon a mitral stenosis, which was believed to be rheumatic in origin.

Chronic renal lesions occurred in 27 cases of this age group. In 11 of these it was the cause of death, 6 presenting diffuse glomerulonephritis and 5 advanced arteriolar nephrosclerosis. Sixteen others had chronic lesions in the kidneys, but died from other causes (7 from rheumatic heart disease). The only other pathologic change which occurred with any notable frequency in this group consisted of lesions in the suprarenal medullæ (in 19 cases). In 2 of these there were adenomatous nodules, in 1 focal necrosis and in 16 chronic focal inflammation in the medullæ. There was splenic follicular hypoplasia in only 4 of this age group. Syphilitic lesions were found in 5 cases; tuberculosis was the cause of death in 4.

Summing up the pathologic findings in these 79 cases, it is readily discernible that chronic renal lesions and rheumatic heart disease occur with entirely too great a frequency in this group to be coincidental. This is further borne out by the fact that in the rheumatic cases the atheromatous changes occurred almost exclusively in the larger pulmonary and coronary arteries and in the ascending aorta, while in the nephritic cases vascular lesions were most striking in the arterioles of the kidneys. In the rheumatic cases there were also atheromatous lesions in the mural and valvular endocardium which closely assimilated the intimal lesions in the arteries.

Only 4 cases of diabetes mellitus came to autopsy during these age periods. All of them had atheromatous lesions in the aorta. Joslin,[2] in 1929, referred to the frequency with which arteriosclerosis was found by the Roentgen ray in diabetic children.

The association of arteriosclerosis with renal lesions in children has been described by many investigators, the earliest writers on the subject being Gull and Sutton,[1] in 1872.

Pappenheimer, Von Glahn[3] and others have described arterial lesions associated with rheumatic heart disease, but the changes which they describe are not the same as the atheromatous lesions dealt with in this study.

Whether or not the lesions encountered in the spleen and suprarenals have any direct relationship to arteriosclerosis has not been ascertained. They certainly occurred with a considerably greater frequency in the atherosclerotic cases than in the nonatherosclerotic cases of the younger age groups.

In 5 cases of far-advanced pulmonary tuberculosis with fibrosis and emphysema of the lungs atheromatous changes were found almost exclusively in the pulmonary vessels. However, there were many cases of tuberculosis in which no atheromatous changes were found.

In every one of the 79 cases presenting atherosclerosis chronic lesions were found in one or more of the viscera, irrespective of the age of the patient.

A discussion of arteriosclerosis in children would be incomplete without reference to the large amount of experimental work being done at present on the subject of hypervitaminosis. It has been conclusively demonstrated experimentally that marked vascular changes with calcification are produced by toxic doses of irradiated ergosterol. That the calcification in the vessels is preceded by lipoid deposition and is identical with the process of atherosclerosis in human beings, has not been so unquestionably proven, although certain investigators claim to have demonstrated the similarity of these lesions by giving less toxic doses, thereby slowing up the process so that the early precalcification stages could be observed. Shelling[4] believes that the toxicity of viosterol depends upon the following factors: (1) Differences in the potency of the irradiated product; (2) age of the recipient; (3) length of time of administration; (4) character of the diet in regard to its content of calcium and phosphorus. It is not known at present whether administration of any of the irradiated products on the market has ever produced vascular lesions in children. It is commonly believed by practitioners and firmly assured by drug houses that therapeutic doses are not harmful. However, caution demands: (1) That administration be kept within the hands of a physician; (2) that in the determination of dosage such factors as diet, age of the patient and degree of need for the irradiated product be carefully considered.

Conclusions. 1. A review of 1070 consecutive autopsies on individuals under 30 years of age revealed atherosclerosis occurring with far greater frequency in connection with certain disease conditions than with others.

2. Rheumatic heart disease was almost invariably accompanied by atheromatous changes in the aorta, pulmonary or coronary arteries.

3. All of the 4 diabetic cases presented atherosclerosis of the aorta.

4. Chronic renal lesions were found in 34 of the 52 nondiabetic nonrheumatic cases which presented atherosclerosis, and were present also in 10 of the 23 rheumatic cases. The renal arterioles were the vessels most frequently involved in these cases.

5. The only other pathologic lesions which occurred with notable frequency in the atherosclerotic group were: (1) Focal lesions in the suprarenal medullæ and (2) hypoplasia of the Malpighian corpuscles in the spleen.

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STUDIES IN ATHEROSCLEROSIS.

II. ATHEROMA AND ITS SEQUELÆ IN RHEUMATIC HEART DISEASE.

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IN the previous paper the strikingly regular association of some degree of atheroma with rheumatic heart disease was brought out. With the hope that an investigation of this association might shed some light on the subject of atherosclerosis, the clinic and pathologic material on all cases of rheumatic fever which came to autopsy during the last 6½ years has been collected and analyzed.

For this report only cases of undoubted rheumatic origin have been included. These numbered 62 (of 3372 autopsies), in each of which either typical active rheumatic lesions were found at autopsy,

or, in the inactive cases, a typical rheumatic history was obtained. The criterion for the former was the presence of verrucous endocarditis, not showing bacteria by the ordinary methods, accompanied by Aschoff nodules in the myocardium and usually associated with a pericarditis. A "typical rheumatic history" included signs and symptoms of cardiac disease accompanying or promptly following an attack of acute polyarthritis. The cases ranged in age from 7 to 66 years, but most of them were under 40 years of age at death. There were 36 males and 26 females, 39 white and 23 colored. Twenty-one cases died as a direct result of the cardiac lesions without any complication other than severe decompensation. The immediate causes of death in the other 41 cases are found in Table 1:

TABLE 1.—CAUSES OF DEATH.

	Number of cases.
Superimposed acute vegetative endocarditis	13
Lobular pneumonia	6
Lobar pneumonia	4
Pulmonary embolus (right atrial thrombosis)	4
Extensive mural thrombosis (left ventricular thrombi, 2; left atrial thrombi, 1)	3
Cerebral embolus	2
Collapse of left lung	2
Coronary occlusion	1
Diffuse glomerulonephritis with uremia	1
Septic abortion	2
Ruptured appendix	1
Cirrhosis of liver (with ruptured esophageal varices)	1
Subarachnoid hemorrhage of undetermined origin	1
Total	41

Methods. In each of the 62 cases there were available for study a pathologic report, microscopic sections stained with hematoxylin and eosin, the original paraffin blocks and extra Zenker material kept in dilute alcohol. In a considerable number of cases the entire heart and occasionally portions of other organs had been preserved in formalin or Kaiserling solution and were available for study. The fat stains used on the latter were (*a*) Herzheimer's Scharlach R,[1] made up with caustic soda, and (*b*) osmic acid, both before and after treating the sections with potassium dichromate. It was found that by slightly modifying the usual osmic acid technique the potted Zenker material permitted a demonstration of lipoids almost as constantly and clearly as the osmic acid-potassium dichromate technique on formalin material. Evidently the dichromate in the Zenker solution fixes the lipoids in such a way that they are not entirely dissolved by alcohol of 60 to 80 per cent concentration even after 6 years.

Generalized arteriosclerosis worthy of note was found in only 15 cases and 12 of these were past 40 years of age. One of the other 3 was 35 years of age and had hypertension. The other 2 were 17 and 33 years of age, respectively.

The incidence of atheroma in the aorta, coronary arteries and pulmonary arteries in these 62 cases of rheumatic heart disease is found in Table 2.

TABLE 2.—INCIDENCE OF ATHEROMA IN RHEUMATIC HEART DISEASE.

Degree of atheroma.	Aorta.	Coronary arteries.	Pulmonary arteries.
Marked	16	12	9
Moderate	31	18	18
Slight	9	14	20
None	2	13	12
No section	4	5	3

The criteria employed for the various degrees of atheroma were as follows:

"Marked"—large, well-formed or numerous atheromatous plaques, or atheroma with calcification.

"Moderate"—numerous atheromatous patches, or small plaques not calcified.

"Slight"—definite atheromatous infiltration but no well-formed plaques or calcification.

"None"—no evidence of atheroma in the intima (in most of the cases in this category only 1 or 2 nonselected sections were available).

The incidence of atheroma in the various age groups is found in Table 3:

TABLE 3.—INCIDENCE OF ATHEROMA BY AGE GROUPS.

Age.	Total number of cases.	Marked atheroma.			Moderate atheroma.			Slight atheroma.			No atheroma.			No sections.		
		Aorta.	Coronary.	Pulmonary.	Aorta.	Coronary.	Pulmonary.	Aorta.	Coronary.	Pulmonary.	Aorta.	Coronary.	Pulmonary.	Aorta.	Coronary.	Pulmonary.
10 yrs. or less	2	0	0	0	1	0	1	0	1	1	0	1	0	1	0	0
11 to 20	10	2	2	1	1	3	2	5	3	2	0	1	4	2	1	1
21 to 30	16	2	1	1	13	3	3	1	4	9	0	7	3	0	1	0
31 to 40	11	0	1	0	6	3	4	3	5	3	1	1	2	1	1	2
41 to 50	11	5	1	3	5	7	5	0	1	3	1	1	3	0	2	0
51 to 60	10	5	5	2	5	2	3	0	0	2	0	2	0	0	0	0
61 to 70	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0
Totals	62	16	12	9	31	18	18	9	14	20	2	13	12	4	5	3

It is to be noted that of 28 cases of rheumatic heart disease in which death from any cause occurred before 31 years of age 25 presented some degree of atheroma in the aorta. In 19 of these there were well-defined plaques (atheroma in the deep intima with superimposed fibrous tissue proliferation). In 4 cases the plaques were large or numerous and some contained calcium. Two of these 4 cases were under 20 years of age. Seventeen of 28 cases also had demonstrable atheroma in the coronary arteries, marked in 3 cases and of moderate degree in 6. The pulmonary arteries were atheromatous in 20 of the 28 cases, markedly so in 2 of them and only moderately in 6.

The question which is raised by these observations is whether or not there is any relation, other than coincidence, between the

rheumatic heart disease and the early development of atherosclerosis. That atheroma occurs in the young unassociated with rheumatic heart disease has been established by many investigators.[2] This group of cases, however, presents a higher incidence of atheromatous changes in the locations noted than has been reported hitherto for the same age group with death from any cause.

There are passing references in the literature to the occurrence of lipoid deposits both inside and outside of vessel walls in rheumatic fever. In his review of the pathology of rheumatic fever, in 1926, Sachs[3] quotes Baehr: "The lime and cholesterin deposits often seen in such vascular lesions are evidence of an atherosclerotic process which has occurred here much more rapidly and far more extensively than elsewhere in the vascular system because of the unusual degree of mechanical strain to which such an abnormal valve is subjected. The destruction of elastica or disarrangement of elastic fibrils as a result of the original inflammatory process evidently results in increased replacement fibrosis and atheroma, as it would elsewhere in the cardiovascular apparatus." Sachs remarks: "Further studies are required to elucidate the precise rôle of chronic inflammation and the factor of strain in the production of rheumatic chronic valvular disease." Pappenheimer and Von Glahn[4] mention atheromatous changes only to assure the reader that the lesions they are describing are not those of atherosclerosis.

It should be emphasized that the pathologic changes discussed here are not the lesions of rheumatic fever in the vessel walls described by Klotz, Pappenheimer, Von Glahn and others. This present report, in no instance, includes under the term "atherosclerosis" those lesions definitely inflammatory in nature so characteristic of rheumatic disease in the vascular tree. Such lesions were found in the great majority of the above 62 cases. The atheromatous changes have not seemed to be particularly related to them, although they frequently occur together in the larger vessels. In the arterioles, however, particularly those at the base of rheumatic valves, which so frequently present proliferative endarteritis, no lipoids have been found.

Von Glahn,[5] Stewart and Branch (cited by Von Glahn) and others have mentioned the occasional deposition of calcium salts in rheumatic lesions. Winkelstein (cited by Sachs) reported calcification and ossification of the pericardium in a case of purulent pericarditis complicating rheumatic heart disease. Since calcification of bloodvessels is usually preceded by atheroma it was considered worth while to investigate the endocardial lesions with special reference to lipoid changes.

In no case was calcification of the endocardium encountered without demonstrable lipoid changes in surrounding areas. In fact, the calcium salts often appeared to be plastered on top of masses of lipoids (Fig. 5). Lipoids, however, were often found without

TABLE 4.—CORRELATION OF CARDIAC LESION WITH DEGREE OF ATHEROMA.

Case No. and age at death.	First known attack of polyarthritis: time before death.	Onset of cardiac symptoms: time before death.	Cardiac lesions.						Degree of atheroma.		
			Myocardium.	Mitral.	Aortic.	Tricuspid.	Pulmonary.	Pericardium.	Aorta.	Coronary arteries.	Pulmonary arteries.
N–25–107 10 yrs.	8 mos.	3 yrs.	Scarred; activity	Scarred	Scarred	n	n	Oblit. fibrous and fibrinous adhesions	Unknown	None	Moderate.
N–25–182 22 yrs.	2 yrs.	2 yrs.	Many scars; activity	Scarred	Scarred	n	n	Oblit. fibrous adhesions	Marked	Slight	Moderate.
N–25–269 21 yrs.	None	4 yrs.	Markedly scarred; activity	Scarred; fungating veg.	Scarred	n	n	Oblit. fibrous and fibrinous adhesions	Slight	None	Slight.
N–26–60 29 yrs.	None	"In childhood"	Scarred; activity	Stenosis	Stenosis	n	n	Hydropericard.; beginning fibrinous exudate	Moderate	Marked	Slight.
N–26–159 27 yrs.	4 wks.	Unknown	Sl. scarred; activity	Scarred; activity	Sl. scarred; activity	n	n	Oblit. fibrinopur. exudate	Moderate	None	None.
N–26–183 18 yrs.	8 yrs.	1 mo.	Marked activity	Stenosis	Activity	n	n	Chr. focal epicarditis; hydropericard.	Slight	Slight	None.
N–26–210 20 yrs.	1 yr.	5 yrs.	Scarred; activity	Stenosis; Str. viridans veg.	Sl. scarred	n	n	No adhesions	Slight	Moderate	Slight.
N–26–229 29 yrs.	8 yrs.	8 yrs.	Scarred; activity	Scarred; sl. stenosis	Sl. scarred	n	n	Oblit. fibrous adhesions	Moderate	Unknown	Moderate.
N–26–332 16 yrs.	3 yrs.	3 yrs.	Scarred	Stenosis	Stenosis	Sl. scarred	n	Oblit. fibrous adhesions	Marked	Moderate	Moderate.
N–26–387 14 yrs.	5 yrs.	Unknown	Activity	Scarred; activity	Scarred; activity	Scarred; activity	n	Chr. focal epicarditis; few adhesions	Slight	Marked	None.
N–27–158 16 yrs.	2 yrs.	3 wks.	Activity	Activity	Activity	Activity	n	Oblit. subacute inflam.	Slight	None	None.
N–27–220 18 yrs.	2 mos.	3 wks.	Activity	Activity	n	n	n	n	Unknown	Slight	None.
N–28–115 23 yrs.	2 mos.	Recent	Activity	Activity	n	n	n	n	Moderate	Moderate	None.
N–28–199 25 yrs.	4 yrs.	4 yrs.	Activity; mural thrombi	Stenosis; activity	Activity	Activity	Activity	Mark. scarred; no adhesions	Moderate	None	Marked.
N–28–340 23 yrs.	Unknown	Unknown	Abscesses; thrombosis	Stenosis; activity	Sl. scarred	n	n	Unknown	Moderate	None	Slight.

25 yrs.			mural thrombi	activity				no adhesions			
N–28–340 23 yrs.	Unknown	Unknown	Abscesses; thrombosis	Stenosis; activity	Sl. scarred	n	n	Unknown	Moderate	None	Slight.
N–29–278 29 yrs.	Unknown	"Years ago"	Markedly scarred	Stenosis; calcification	n	n	n	No adhesions	Moderate	Slight	Slight.
N–29–330 22 yrs.	"Repeated attacks for years"	"Early childhood"	Mural thrombi	Scarred; activity	n	Scarred; activity	n	No adhesions	Moderate	Moderate	Moderate.
N–29–457 13 yrs.	6 wks.	5 wks.	Activity	Sl. scarred; activity	Activity	n	n	Oblit. organizing fibrinous exudate	Slight	Unknown	None.
N–29–541 17 yrs.	7 mos.	Unknown	Sl. scarred; activity	Activity	Activity	Activity	Activity	No adhesions	Marked	Slight	Slight.
N–30–246 27 yrs.	8 yrs.	Several years	Markedly scarred; activity	Stenosis; fungating veg.	Scarred; fungating veg.	Scarred; rheumatic activity	n	Fibrous and fibrinous adhesions	Moderate	None	Slight.
N–30–407 26 yrs.	"Repeated attacks for many years"	Over 4 yrs.	Scarred	Sl. scarred; fungating veg.	Sl. scarred; fungating veg.	n	n	n	Moderate	Moderate	Slight.
N–30–576 17 yrs.	"Growing pains"	12 yrs.	Markedly scarred	Stenosis	Stenosis; calcification	n	n	No adhesions; chr. epicard.	Unknown	Marked confluent plaques	Moderate.
N–31–69 17 yrs.	None	2 yrs.	Diffusely scarred	Stenosis; calcification	Stenosis; calcification	Scarred; early stenosis	n	Hydropericard.	Moderate	Moderate	Marked.
N–31–71 26 yrs.	Unknown	Unknown	Activity	Activity; also bac. endocardium	n	n	n	n	Moderate	None	Slight.
N–31–118 25 yrs.	Unknown	Unknown	Markedly scarred; activity	Scarred	Scarred	n	n	Oblit. fibrous and fibrinous adhesions	Moderate	Slight	Slight.
N–31–194 24 yrs.	"Repeated attacks since early childhood	18 yrs.	Markedly scarred	Stenosis; calcification	Scarred	Stenosis; calcification	Scarred	Oblit. organizing adhesions	Marked	Slight	Slight.
N–31–300 7 yrs.	3 mos.	1 wk. (?)	Activity	Activity	n	n	n	Oblit. fibrinopur. exudate	Moderate	Slight	Slight.
N–25–260 30 yrs.	13 yrs.	5 yrs.	Activity	Stenosis	Sl. scarred	n	n	Hemopericardium	Moderate	None.	None.

calcium salts being present. Frequently the lipoid droplets occurred in parallel rows, apparently following the course of degenerating elastic fibers. This appearance has been noticed frequently in atheromatous aortas. At other times the droplets occurred inside endothelial cells, particularly those covering the ventricular surface of the mitral valve (Fig. 3). Lipoid changes were observed not only in the valvular endocardium but also in the lining of the left atrium, most frequently in the elastic layer of areas involved in rheumatic endocarditis.

These lipoids stained readily with Scharlach R and with osmic acid. They were found to be doubly refractile under the polarizing microscope. Occasionally cholesterin crystals were present in the lipoid masses. These remained unstained by the Zenker-osmic acid technique (Fig. 4). By none of the methods employed could any difference be detected between the atheromatous changes occurring in the endocardium of young individuals suffering from rheumatic heart disease, and those changes in the aorta which are commonly found in much older individuals.

In Table 4 the degree of atheroma is checked against the extent and duration of cardiac involvement and the age of the patient.

Just as there is no constant relationship between the extent of the cardiac lesions and the duration of the rheumatic disease, so the degree of atheroma cannot be predicted from these facts. Undoubtedly that elusive quality called individual susceptibility plays a large rôle in the development of atheroma in rheumatic disease. A familial, if not actually an hereditary factor, has long been suspected in both rheumatic disease and atherosclerosis. Nevertheless, the degree of atheroma in many of these cases can be seen to correspond more or less to the severity of the disease as judged by the other data given in the table.

At just which stage of the disease the atheromatous changes begin is uncertain. In Case N–31–300, aged 7 years, and having a reliable history of rheumatic disease of not more than 3 months' duration with cardiac involvement for a much briefer period, there were a few yellow plaques in the ascending aorta large enough to be easily visible to the naked eye. There was no valvular stenosis, yet lipoids were readily demonstrable microscopically in the pulmonary arteries. Case N–31–71, a much older patient, but with lesions very similar to those of the preceding case, presented about the same degree of atheroma in the aorta and pulmonary arteries.

Negative or inconsiderable findings of atheroma in the preceding tables possess relatively little significance because the only sections available in many of these cases were taken merely as a matter of routine, without particular regard for atheromatous plaques, and these were stored later in alcohol. That atheroma in rheumatic disease is even more frequent and more marked than indicated in the above tables has been proven by autopsies performed since the beginning of this investigation.

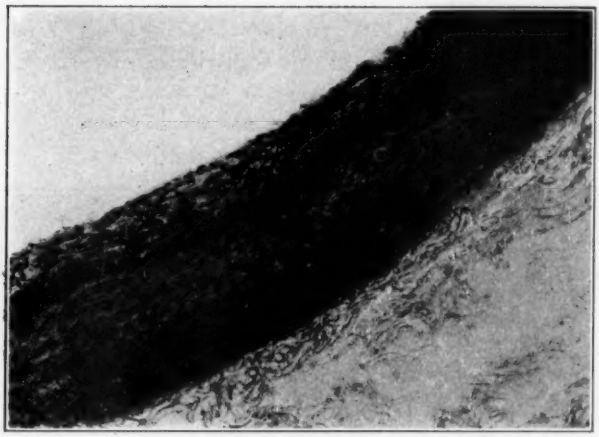

FIG. 1.—Large pulmonary artery with intima loaded with lipoids. Case N–31–69, aged 17 years. Scharlach R—hematoxylin.

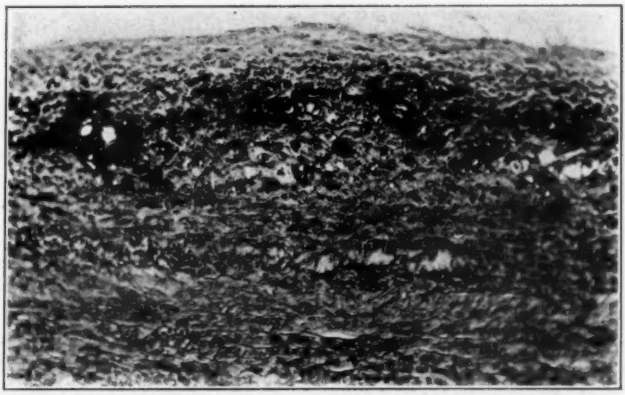

FIG. 2.—Aorta with intima loaded with lipoids. Note elastica interna. Case N–26–332, aged 16 years. Zenker-osmic Giemsa.

FIG. 3.—Mitral valve with very early lipoid infiltration. Note lipoids inside endothelial cells. Case N–31–71, aged 26 years. Zenker-osmic Giemsa.

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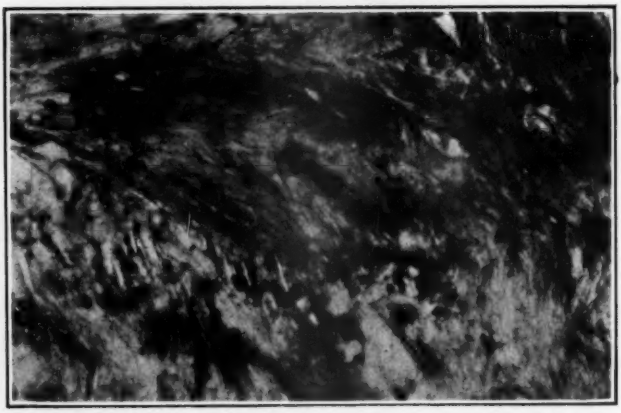

FIG. 4.—Mitral valve with lipoid infiltration. Note unstained cholesterin crystals. Case N–26–159, age 27 yr. Zenker-osmic-Van Gieson.

FIG. 5.—Mitral valve with lipoid infiltration and extensive calcification. Case N–31–69, aged 17 years. Scharlach R—no counterstain used.

Because of the difficulties in obtaining reliable "negative" material, control cases are presented here with some reservation. It may be stated with assurance, however, that in the hundreds of cases under 30 years of age which have been examined microscopically for atheroma, and material from which has been preserved in a similar manner, the incidence of atheroma, in the group as a whole, is decidedly lower than that in the rheumatic cases.

There are 2 cases, however, which will be cited because of their particular value as controls.

Case Abstracts. N–29–399, a white girl, aged 11 years, suffered a severe abrasion over the right eye. Subsequently she developed hemolytic streptococcus septicemia and died 6 weeks after the accident. The autopsy findings were multiple abscesses in the viscera with streptococcus vegetations on the mitral and tricuspid valves, with septic pulmonary infarcts. No evidence of atheroma, either gross or microscopic, was found anywhere. A reliable history and a complete autopsy presented no evidence of rheumatic disease.

N–31–87, a negro, aged 30 years, was admitted to the hospital complaining of painful, swollen joints of 2 weeks' duration. He had never had a previous attack, but had suffered from tonsillitis for years. Physical examination was essentially negative except for the signs of acute polyarthritis involving both ankles, the right wrist and right shoulder. Shortly after admission the patient developed lobar pneumonia and died. At no time were there any signs or symptoms of rheumatic heart disease. The autopsy findings were essentially negative except for lobar pneumonia and acute polyarthritis. No rheumatic lesions were found in the heart and there was no evidence of atheroma either gross or microscopic.

Is atheroma in rheumatic disease a transient phenomenon or is it progressive? Whether or not the lipoids are ever reabsorbed has never been determined. However, one fact established beyond any doubt is that there is a decided tendency for atheromatous areas to become calcified. Case N–31–69 was under observation and treatment for over 2 years. The course of the rheumatic disease was carefully studied as it progressed from valve to valve. At autopsy the location of the calcified areas on both the mitral and aortic valves was demonstrably in atheromatous lesions (Fig. 5). It was this case which furnished the first convincing link between the suspicion and the proof that calcified stenotic valves found in adults are rheumatic in origin. This subject will be discussed more fully in a subsequent report.

Are the lipoid deposits in rheumatic heart disease limited to valvular endocardium and the intima of the aorta, coronary and pulmonary arteries? In these 28 cases under 31 years of age no other vessels were affected with any regularity. In a considerable number of patients dying during an active rheumatic attack, an acute or subacute polyserositis was found, and in some of these there were remarkable lipoid deposits beneath the exudate, in the splenic capsule, in the pleura and, in 1 case, within and beneath the mesothelial cells of the uterine peritoneum. In some of these

same cases there were considerable lipoid deposits in the tubular epithelium of Henle's loops in the kidney.

Many other questions have been raised by these observations which cannot be answered at the present time. Why do atheromatous changes occur particularly in mesodermic tissues? What does rheumatic disease have in common with the relatively few other conditions which are found to predispose to the early development of atherosclerosis?

Summary. 1. Sixty-two cases of rheumatic heart disease have been analyzed with reference to the incidence of atheroma, particularly in the aorta, coronary and pulmonary arteries.

2. In 28 cases under 31 years of age the degree of atheroma has been compared with the duration and extent of the cardiac lesions.

3. Rheumatic heart disease has been found to predispose to the early development of atheromatous lesions in the aorta, pulmonary and coronary arteries, and also in the valvular and left atrial endocardium. Lipoid deposits also have been found, in some cases, in the inflamed serous membranes and in certain renal tubules.

4. Lipoid deposition has seemed to begin soon after the onset of cardiac disease, and, in a very general way, has paralleled in degree the cardiac lesions.

5. The atheromatous changes, in many cases, have been progressive, leading to calcification and, when in the valvular endocardium, accentuated stenosis.

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THE PROGNOSTIC VALUE OF REPEATED BLOOD CULTURES IN PNEUMOCOCCUS LOBAR PNEUMONIA.

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In acute infectious diseases such as pneumococcus lobar pneumonia the demonstration of a bacteremia by blood culture is of clinical value only under two conditions: (1) The information gained should be of benefit to the patient and the physician; (2) the culture method should not be complicated and yield results within 18 hours or less. While knowledge concerning the prognosis is not necessarily valuable *per se*, it becomes a matter of definite

practical interest, when the efficiency of a mode of treatment is to be evaluated.

Reports on the incidence of bacteremia in lobar pneumonia vary. Rosenow reported the presence of bacteria in the blood stream in 91 per cent of a series of patients, while other authors cultivated pneumococci in but 20 to 30 per cent of their patients.

The presence of a few bacteria in blood samples taken at frequent intervals and cultivated by refined methods should certainly be distinguished from a bacteremia readily shown in 1 or 2 cc. of blood. Some years ago it was pointed out by Sutton and Sevier,[1] and later again by Rosenblueth,[2] that for comparison purposes the separation of patients by blood culture into positive and negative groups is too arbitrary and ignores the degree of bacterial invasion, which is really the more important factor.

In the present investigation an attempt has been made to determine by a simple technique requiring small amounts of blood the degree of pneumococcus blood stream invasion and its changes in patients admitted to the hospital.

Method. The blood culture method consisted of inoculating 2 cc. of whole blood into 50 cc. glucose glycerophosphate broth at the bedside of the patient. At the same time an agar plate was poured with 1 cc. of patient's blood. Blood was always obtained from the same arm vein.

The glycerophosphate medium is prepared as follows: To veal-heart infusion add 1 per cent Difco peptone, 0.5 per cent NaCl and 1 per cent sodium glycerophosphate (anhydrous, powdered, Mallinckrodt). Boil for 1 hour, filter, autoclave for 20 minutes at 15 pounds' pressure and add 1 per cent glucose in sterile solution. The addition of glycerophosphate serves three purposes: The reaction of the medium is automatically brought to pH 6.8 to 6.9, no titration being necessary; the substance acts as a buffer and enriches the medium by its content of glycerin. Disodium glycerophosphate as a buffer was introduced by Mellon, Acree, *et al.*[3] in 1921, and has proved its value as indicated during the interval. Moreover, this broth is more resistant to hydrogen-ion change when autoclaved at pH 8 than are media buffered with other phosphates. In addition, calcium and magnesium salts of glycerophosphate are soluble.

Pneumococci present in the blood stream to such a degree that one or more organisms appear on the blood plate inoculated with 1 cc. of patient's blood grow with a definite and characteristic change of the broth during 16 hours' incubation at 37° C. The medium becomes turbid throughout and has a dark greenish-brown color. If the degree of bacteremia is small, and no colonies are seen on the plate, the characteristic changes of the medium appear after 24 to 72 hours' incubation. Experience has shown us that the blood culture can be considered sterile if no growth appears after 72 hours' incubation.

The upper layer of a positive culture (or a centrifuged specimen, if the culture was shaken up) is used for the determination of the pneumococcus type. Distinct and specific precipitation takes place with type precipitin serum in a water bath at 56° C. within 1 to 10 minutes or often even at room temperature without incubation, if the tubes containing the culture-serum mixture are shaken for a few minutes. It happened in several instances that the blood culture precipitated Types I or II serum, while repeated sputum examinations from the same patient yielded only Type IV pneumococcus. But it was never observed that the blood culture was

Type IV when we recovered Types I or II from the sputum of the same patient. Diagnostic sera vary in their flocculation ability to a considerable degree; a very satisfactory serum was prepared in rabbits by the method described by Cole and Moore.[4]

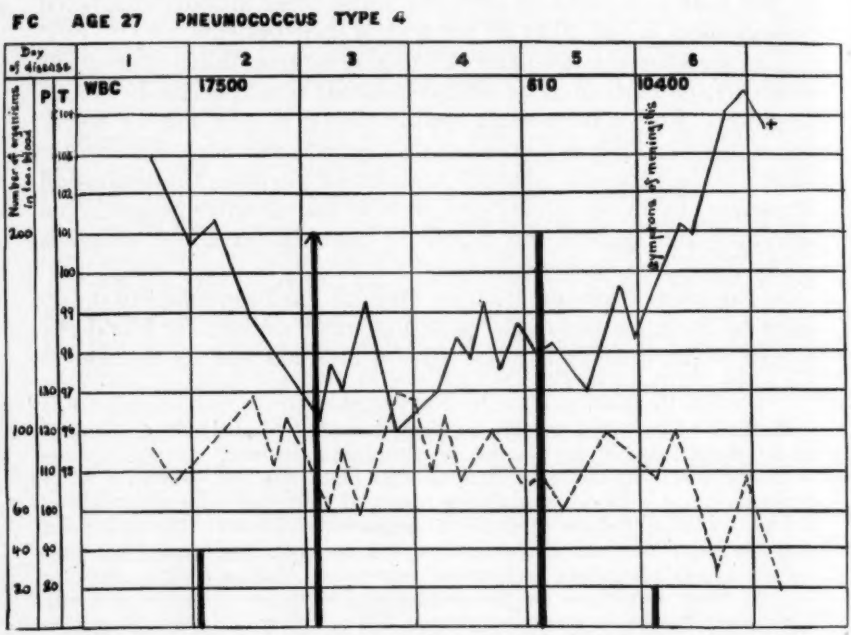

CHART I.—F. C., a white man, admitted to the hospital with pneumococcus Type IV lobar pneumonia. Columns indicate degree of bacteremia. The patient developed symptoms of meningitis on the 6th day and died 24 hours later of pneumococcus meningitis.

Results. This report is based upon the examination of blood cultures taken from 139 pneumococcus pneumonia patients during the first five months of 1931. Symptomatic treatment varied and followed the generally recognized procedures of therapy, although none of the patients was treated with antipneumococcus serum. From 45 patients a positive blood culture was obtained in one or more instances. A percentage of 32.4 per cent positive blood cultures compares favorably with the results obtained by other authors (Rosenblueth, 22.4 per cent; Schottmueller, 23 per cent; Cole, 27 per cent; Cecil, 29.7 per cent; MacLachlan, Kastlin, Lynch, 29.7 per cent. It seems justifiable to conclude that the technique used in this investigation is not less efficient than other methods, although the culture medium used is slightly acid. The mortality rate in our patients with positive blood cultures was 75 per cent. Cecil reported 78 per cent; Cole, 67 per cent; Rosenblueth, 85 per cent; MacLachlan, Kastlin and Lynch, 73 per cent. The distribution of types was as follows: Positive blood cultures: Type I, 18;

Type II, 22; Type IV, 5. In patients with negative blood cultures sputum examinations yielded Type II as often as Type I. Although Type III was not observed during the season, the incidence of positive blood cultures and the mortality rate in such patients correspond well with data furnished by several authors. The series under observation can, therefore, be considered as representing average cases.

Whenever a patient was admitted to the hospital with the diagnosis of pneumonia a blood culture was obtained by the method mentioned above. The degree of bacteremia, when present, was determined by counting the number of bacteria on the agar plate inoculated with 1 cc. of patient's blood. From the patients showing a bacteremia at admission daily blood cultures were obtained until the change in the degree of bacteremia was clearly indicated or the blood stream became sterile. From the series of 45 patients with a positive blood culture 14 were eliminated from consideration, because only 1 blood culture was obtained. Most of them died, before a second blood culture could be secured.

It was found that 20 patients showed an increasing or stationary number of pneumococci in the blood stream. None of the patients survived; the mortality in these patients was 100 per cent irrespective of the stage of the disease, the time of admission to the hospital or the degree of bacteremia, when the first blood culture was taken.

The increasing degree of bacteremia predicted a fatal outcome, from 1 to 10 days preceding death. That the increasing number of bacteria in the blood stream can be a more definite indicator of the prognosis than the general reaction of the patient is illustrated in the chart of the patient F. C. The patient died on the fourth day after the increase of bacteremia had been demonstrated.

TABLE 1.—PATIENTS WITH AN INCREASING OR STATIONARY DEGREE OF BACTERIA.

Type.	Name.	Age.	Onset.	Day of disease.										
				2.	3.	4.	5.	6.	7.	8.	9.	10.	11.	14.
I.	F. C.	?	Acute.	40	200	...	200	20	D					
	T. O.	40	3 with cold	..	...	...	60	180	D					
	C. E.	28	3 with cold	1	30	300	D							
	M. B.	55	Acute	..	..	...	...	2	30	200	D			
	A. K.	45	Acute	..	...	...	...	1	120	...	...	...	D	
	O. M.	27	Acute	40	200	...	...	...	...	D				
	W. K.	32	Acute	..	...	...	Neg.	...	...	...	35	100	..	D
	R. C.	50	Acute	..	...	1	100	...	D					
	J. N.	37	Acute	30	...	30	D							
	L. B.	?	?	..	...	...	40	150	D					
II.	M. W.	25	Acute	..	...	...	...	...	...	1	100		D	
	S. J.	?	?	..	...	...	20	...	200	D				
	J. W.	30	2 with cold	..	...	...	...	...	1	200	D			
	T. G.	46	1 with cold	1	30	200	...	...	...	...	...	...	..	D
	J. C.	55	Acute	..	...	...	1	30	30	30	125	125	D	
	W. S.	28	Acute	..	...	1	20	200	D					
	B.	?	?	..	...	...	200	200	D					
	E. F.	34	Acute	..	3	3	40	D						
	P. S.	?	?	..	...	...	5	100	...	D				
IV.	E. L.	35	Acute	..	...	...	...	...	40	200	D			

Figures designate number of pneumococci per 1 cc. of blood. D = Death.

In 11 patients the degree of bacteremia decreased from day to day; 2 patients died (mortality, 17 per cent).

TABLE 2.—PATIENTS WITH A DECREASING BACTEREMIA.

Type.	Name.	Age.	Onset.	Day of disease.									
				1.	2.	3.	4.	5.	6.	7.	8.	9.	10.
I.	E. P.	32	Acute	..	...	20	Neg.	...	...	...	...	D	
	C. E.	?	Acute	..	...	10	10	Neg.	...	Reco	vered		
II.	T. E.	30	Acute	..	20	10	1	Neg.	...	Reco	vered		
	W. S.	30	Acute	..	..	30	10	..	1	1	Neg.	..	Recovered
	E. L.	38	Acute	..	30	20	1	..	1	Neg.	Neg.	..	Recovered
	J. M.	?	Acute	..	..	1	Neg.	..	Reco	vered			
	M. V.	50	Acute	5	Neg.	..	Reco	vered					
	E. J.	?	Acute	..	1	1	Neg.	..	Reco	vered			
	J. H.	40	Acute	..	2	1	D						
	M. W.	35	Acute	1	4	Neg.	Neg.	..	Reco	vered			
	J. K.	16	Acute	..	1	Neg.	..	Reco	vered				
IV.	W. K.	38	Acute	..	1	Neg.	..	Reco	vered				

Figures designate number of pneumococci per 1 cc. of blood. D = Death.

In 1 patient, A. S., aged 60 years, we observed a decrease from 50 organisms in 1 cc. of blood to 25 in the second blood culture and no growth in a third blood culture; the patient failed to show clinical improvement; a bacteremia reoccurred later and at autopsy it was found that the patient had developed a pneumococcus endocarditis.

It is interesting to note that in none of the patients with a decreasing number of pneumococci in the blood stream and recovering from the infection the initial bacterial count exceeded 30 colonies per 1 cc. of blood. Considering the possible technical errors in adding the exact amount of 1 cc. of blood to the agar plate, this figure confirms what Rosenblueth[2] reported previously: "We have not seen recovery in any serum untreated patient with more than 28 colonies per 1 cc. of blood." The experience that none of the patients with more than 30 organisms in the blood stream survives suggests that at least in the stage where the organisms enter the blood stream the number of organisms rather than variations in the virulence of the individual strains plays the major part in breaking down the resistance of the patient. Such consistence in the maximum degree of bacteremia which a patient can overcome could not exist if the virulence of the pneumococci would differ materially. This observation substantiates experimental findings of Whittle[5] and of Gundel and Wasu,[6] who tested the virulence of pneumococcus strains recovered from the sputum and empyemas of Types I and II lobar pneumonias. They found that such pneumococci are uniformly highly virulent. The relationship of the number of bacteria in the blood stream to resistance suggests further that the active factor, leading to the fatal outcome, is not an exotoxin, but either a so-called endotoxin or toxic products derived from the action of pneumococci upon body tissues.

TABLE 3.—RELATION OF STAGE OF PNEUMONIA, WHEN BACTEREMIA WAS FIRST DEMONSTRATED TO TREND OF BACTEREMIA.

		Bacteremia first demonstrated after onset of pneumonia.	
		Within 1 to 3 days.	After 3 days.
Number of patients with	Increasing bacteremia	6	14
	Decreasing bacteremia	12	1

TABLE 4.—DISTRIBUTION OF PNEUMOCOCCUS TYPES AMONG PATIENTS SHOWING AN INCREASING AND DECREASING BACTEREMIA.

		Pneumococcus types.		
		I.	II.	IV.
Number of patients with	Increasing bacteremia	10	9	1
	Decreasing bacteremia	2	10	1

When the patients are listed according to the stage of disease at admission to the hospital it is found that a bacteremia with an increasing number of bacteria occurs more often after the third day of disease, while the patient, who has a decreasing bacteremia has the bacteremia in the early stages of the disease. Type I pneumococcus showed more tendency to increase than to decrease in our series. However, all these factors are less constant and of lesser value for predicting a prognosis than a determination of the degree of bacterial invasion and its trend. In most patients with a positive blood culture and a bacterial count below 30 organisms per 1 cc. of blood a second blood culture taken within 24 hours after the first one indicates clearly the change in the degree of bacteremia.

Summary. 1. The degree of bacteremia and its course have been determined by a simplified repeated blood culture method in a number of pneumococcus pneumonia patients, not treated with antipneumococcus serum. The method employed requires 3 cc. of blood and gives results within 16 hours, if the degree of bacteremia is one or more organisms per 1 cc. of blood.

2. Of 20 patients who had an increasing or stationary degree of bacteremia none survived.

3. In the series of 12 patients in whom the bacteremia decreased and disappeared 10 recovered.

4. In none of the patients who overcame the infection did the maximum degree of bacteremia exceed 30 organisms per 1 cc. of blood at any time.

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INTERNAL DRAINAGE.

A Factor in the Production of Postoperative Massive Collapse of the Lung (Pulmonary Atelectasis). Suggestions as to Prevention and Treatment.

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Any theory which is offered to explain the production of postoperative massive collapse of the lung must account satisfactorily for the varied onset of the condition, diversity of signs and symptoms, predilection of sites, extensiveness, migrations, recurrences and response to various treatments.

The study of atelectasis as it has occurred both following and independent of surgical procedures leads us to believe that the cause and entire clinical picture can be explained on a combined mechanical and infectious basis. It is due to the presence of excess intrabronchial secretions and the influence of "internal drainage" upon these secretions.

By internal drainage, we mean the spilling of material from place to place within the tracheobronchial tree. Such spilling actually occurs, follows definite laws, spreads infection, obstructs bronchi and interferes with the air flow to the lung. This has been proved repeatedly by physical examination, Roentgen ray, iodized oil injection, bronchoscopic inspection, operative findings and autopsy examination[1] Figs. 1 to 4.

The sites at which the intrabronchial secretions collect, manifest abnormal physical findings and produce pulmonary atelectasis are dependent on: the amount, virulence and viscosity of the secretions; the relative position of the various bronchial openings; the course of the bronchial stems; the posture of the patient; and the length of time that the patient remains in a given position.

Source of Excess Intrabronchial Secretions. In patients with pulmonary tuberculosis, asthma, bronchiectasis and pulmonary abscesses, excess secretion or exudate is already within the trachea and bronchi before any type of surgical intervention is instituted; but in those who have had no previous pulmonary disease, the secretions are aspirated from the mouth and nasopharynx dur-

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ing and immediately following the operation. This aspiration is more common than is generally supposed and can occur with all types of anesthesia or even in the unanesthetized.

Evidence of Aspiration. Contrary to general opinion, the cough reflex is rather inefficient in prohibiting the entrance of foreign material into the trachea and bronchi; for iodized oil can be introduced through the mouth into the lungs of unanesthetized patients, and lipiodol instilled into the nares during sleep is found in the bronchi on Roentgen examination the following morning.[2] The observations of Mandelbaum,[3] which were confirmed by us, add further evidence regarding the frequency of aspiration in the unanesthetized. He noted on bronchoscopic examination that the bronchial mucous membrane was definitely stained after dye had been introduced into the nares of wide awake and unanesthetized patients 8 to 10 hours previously. The high incidence of aspiration during general anesthesia is proven convincingly by the experimental and clinical studies of Lemon[4] and Myerson.[5] Seventy-nine per cent of Myerson's cases had blood in the trachea or bronchi following tonsillectomy even though the average duration of the operation was 9 minutes.

In 2 patients who had been operated upon in the sitting position under ether anesthesia for the relief of paranasal sinus conditions, we found blood in the bronchi of both lungs but especially the right. This material had drained down from the operative area, and had it not been removed, probably both of these patients would have developed atelectasis or other pulmonary complications; for considerable data have accumulated which show the rôle that increased intrabronchial secretions or materials play in the production of postoperative pulmonary atelectasis.

Evidence that Increased Intrabronchial Secretions Cause Atelectasis. In addition to Jacobaeus,[6] reports of atelectasis following the introduction of iodized oil into the bronchi and after pulmonary hemorrhages, we have noted that the condition is not uncommon in unoperated and unanesthetized patients with pulmonary abscesses. In our cases, the atelectasis occurred at the area to which the pus could most readily spill by internal drainage. A right basal abscess produced a left-sided atelectasis when the patient lay on the left side for a period of time; but upper lobe abscesses led to atelectasis at the corresponding bases when the patient was in the semi-Fowler position. The part that increased intrabronchial secretions and exudates played in the production of the atelectasis was demonstrated clearly on bronchoscopic examination, for pus was found in the bronchi leading to the atelectatic areas, and the atelectasis disappeared as soon as the pus was removed.

In these patients with iodized oil injections, pulmonary hemorrhages and pulmonary abscesses, the onset of the atelectasis, as well as the symptoms, physical findings, roentgenologic changes.

bronchoscopic findings and response to treatment was essentially the same as that seen in the type of atelectasis that follows surgical procedures. Both the surgical and the nonsurgical atelectases were due to one of the following types of bronchial occlusion: thick plugs of inspissated pus, films of viscid mucoid material, inflammatory edema, or thin secretions that had run deeply into and filled the minor bronchial stems. Our observations lend support to the work of Elliott and Dingley,[7] Coryllos and Birnbaum,[8] Jackson and Lee,[9] and Julian Moore.[17]

Previously, too much emphasis was placed on the importance of the thick plugs, and not enough attention was given to the other types of bronchial occlusion. In this respect, Sante[10] reports a case of atelectasis that is worthy of mention because on first sight, it appears to be due to a cause other than bronchial obstruction. His opinion was based on the fact that the condition cleared up completely after postural drainage even though no bronchial plugs had been seen on bronchoscopic examination and no improvement had followed the bronchoscopic treatment. The sequence of events can be understood in this instance when we appreciate that atelectasis can be caused by thin secretions that run deeply into the minor bronchial stems. This type of material cannot be seen on bronchoscopic examination but can be spilled out of the small bronchi by postural drainage. We have proved this experimentally, and Julio Diez[11] has confirmed it on autopsy examination. In Diez's cases of postoperative atelectasis, plugs were found in the minor bronchial ramifications when not seen in the major bronchial stems.

With the bronchoscope in place, it has been observed that secretions can alter in both form and position either spontaneously or following cough and postural drainage exercises. We have seen viscid filmy secretions, that were occluding a bronchial opening, break loose suddenly from their attachments to the upper bronchial wall and retract like an elastic band into an apparently innocent and insignificant position on the floor of a larger bronchus. This unplugging of the bronchus and reëstablishment of the air flow took place in spite of the fact that nothing was expectorated.

With this understanding of the behavior of intrabronchial secretions and the types of bronchial plugging, we are now in a position to discuss the clinical phases of postoperative atelectasis.

Postoperative Atelectasis. *The Onset and Severity of Symptoms.* The obstruction of the bronchial openings by secretions is more or less a matter of chance; for it may not occur at all or it may take place during any phase of respiration. If a large bronchus is occluded at the end of expiration when the lung is already diminished in air content, there will be a rapid onset of the atelectasis, sudden and marked reduction in the vital capacity, marked increase in the negative intrapleural pressures, retraction of the mediastinal structures toward the involved side and the production of serious and alarming

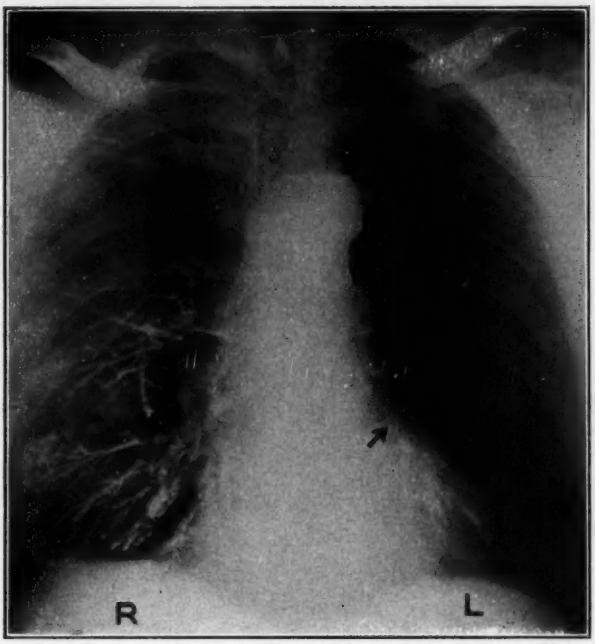

FIG. 1.—Iodized oil introduced through the mouth into the tracheobronchial tree without the use of any type of anesthesia. Note the bulk of the oil in the right lung.

FIG. 2.—Internal drainage. Same patient as Fig. 1. The oil spilled from the right lung into the left after the patient lay on his left side for a few minutes. Posture determined this spilling. There was no cough and none of the oil was expectorated.

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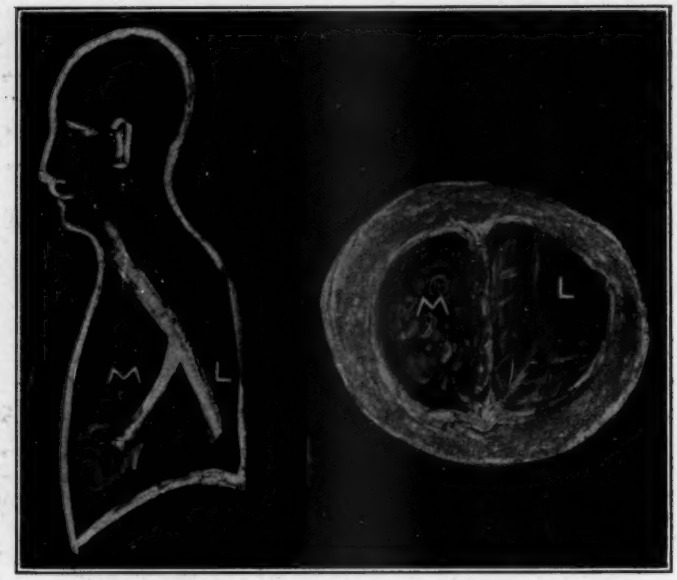

FIG. 3.—Sketch of a middle lobe abscess and the bronchoscopic appearance when the patient is in the erect position. The middle lobe bronchus (*M*) runs anteriorly while the lower lobe bronchus (*L*) passes posteriorly. There is neither adequate drainage of pus or spilling into the lower lobe bronchus when the patient is in this position.

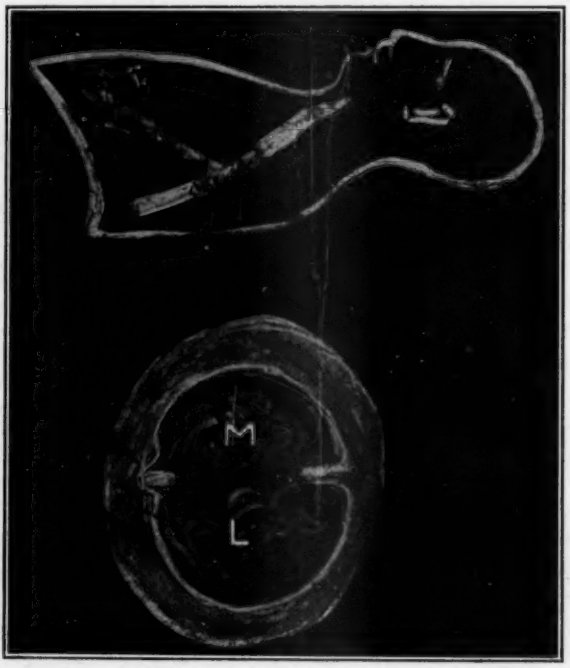

FIG. 4.—Internal drainage. Note the changed conditions when the patient lies flat on his back. The pus now spills from the middle lobe bronchus (*M*) to obstruct the air flow to the lower lobe bronchus (*L*). This mechanical spilling following changes in posture is important not only in lung abscesses but also in considering the migrations, recurrences and treatment of atelectasis.

FIG. 5.—Diagram showing the minor bronchial openings of the right lower lobe which are most frequently obstructed by aspirated secretions, and the corresponding areas upon the chest where abnormal physical signs are elicited. (*b*) The most frequent site of atelectasis and (*a*) the posterior minor bronchus that supplies this area. (*M*) middle lobe.

FIG. 6.—Lipiodol injection of the right lung. The upper lobe bronchus (*RU*) arises at an angle of 90 degrees from the side wall of the main stem bronchus; and if secretions are to flow into this lobe, the patient must be lying flat on his right side.

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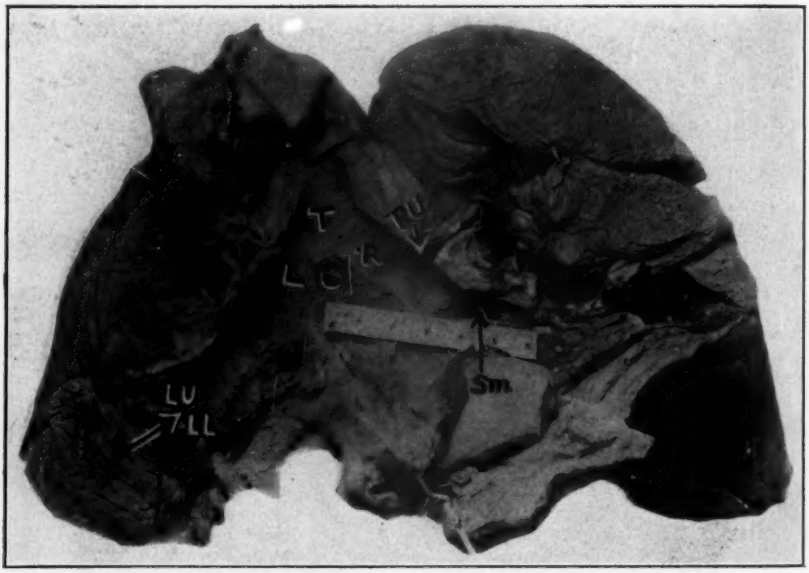

FIG. 7.—Specimen illustrating the anatomy of the tracheobronchial tree, the free communication between the bronchial trunks, and the opportunities for the spilling of intrabronchial material from one trunk to another. Atelectatic migrations take place in this manner. *T*, trachea; *RU*, right upper lobe bronchial opening directly across from the bifurcation of the trachea (*C*); *R*, right main bronchus; *L*, left main bronchus; *Sm*, septum between the middle and right lower lobe bronchial openings; *S*, septum between the left upper (*LU*) and left lower lobe bronchial openings (*LL*).

symptoms. Should the bronchus be plugged at the end of inspiration, however, an obstructive emphysema ensues first and the onset of the atelectasis is gradual and delayed depending on the rate of absorption of the trapped air. Accordingly, the symptoms are more gradual in onset and decidedly less severe.

The symptoms are no exact guide to the extensiveness of the atelectasis but are determined by the suddenness and amount of reduction in the vital capacity and the severity of the associated intrabronchial infection. A gradual reduction in the vital capacity, even though of high degree, can be tolerated much better than a less marked but more sudden alteration. This is particularly applicable to those patients with extensive atelectasis and practically no symptoms.

It is the occasional suddenness of the onset and the similar type of recovery that have led to the suggestion that the etiologic factors were on a vasomotor, phrenic, vagus, or sympathetic reflex basis; but these theories have never been proved and we have found no evidence to support them. Likewise, the early suggestion of Pasteur[12] that the elevation of the diaphragm was responsible for the atelectasis is now abandoned, for the high diaphragm is a result and not a cause of the condition. The atelectasis in Pasteur's cases, appears to us, to be explained best on a basis of aspiration and the internal drainage of these aspirated secretions throughout the lungs; because his deductions were based on the study of debilitated patients suffering from postdiphtheritic paralyses. These are the types most likely to aspirate material and least likely to expectorate it.

Type and Extensiveness. As has been shown in discussing the behavior of intrabronchial secretions, thin material enters the minor bronchial openings and produces a patchy or lobular atelectasis; whereas, the thicker more viscid material is likely to plug a larger bronchus and produce a lobar atelectasis.

Predilection of Sites. It is interesting to note the regularity with which postoperative atelectasis occurs at certain sites and to find that these areas are identical with those at which lipiodol, blood and pus collect when the patient is in a given position. The influence of posture in predetermining the site of the atelectasis is shown especially following operations upon the kidney. In such cases, when postoperative pulmonary complications occur, they involve the lung that is opposite from the side of the diseased kidney. On first sight, this appears to support Briscoe's[13] theory of compression of the chest wall and interference with the muscles of respiration as the primary factor in the production of atelectasis; but we believe that the compression of the chest wall is a contributing rather than a primary factor and that the atelectasis will not occur if excess secretion is not present within the tracheobronchial tree. The aspirated secretions spill into the lung that is in a dependent position during and following the operation and account for the atelectasis

at a particular site. The same principle applies following operations upon the chest. The atelectasis does not necessarily occur on the side that is tightly strapped and on which there is an interference with the muscles of respiration, but rather at the site to which the collected secretions drain and obstruct bronchi. By the compression theory, it would be difficult to explain the incidence of atelectasis at the right base especially when the operation is upon a distal portion of the body and when there is no compression of the chest wall or interference with the muscles of respiration.

The frequency of involvement at the right base is due in fact to the anatomical features which render this bronchus accessible to secretions, and to the semi-Fowler or elevated postoperative posture which permits the drainage into the lower lobe. Bradford[14] has called attention to the frequency of minor degrees of atelectasis at the area lying below the angle of the right scapula. This is easily understood. The first available opening reached by small amounts of thin aspirated material is the posterior minor bronchus of the right lower lobe, and this leads to the area described by Bradford (Fig. 5).

The inability of intrabronchial secretions to flow into the upper lobe bronchial openings when the patient is in the semi-Fowler position accounts for the infrequency of isolated upper lobe involvements. All of the cases of isolated right upper lobe atelectasis that we have seen were in the supine position and usually lying upon the right side. In other words, they were in the position that facilitated best the spilling of secretions into this upper lobe. If the right upper lobe is to become involved, the patient must be in the same position that is employed when filling this lobe with lipiodol (Fig. 6). The same general principles apply to bilateral basal atelectases.

Migrations and Recurrences. The spilling of intrabronchial secretions by internal drainage accounts also for the types of atelectasis that show migrating and recurring tendencies (Fig. 7). When patients with right upper lobe atelectasis are changed from the supine to the semi-Fowler position and instructed to take deep breaths, the signs of the atelectasis disappear from the upper lobe and begin to appear over the corresponding lower lobe. We have seen migrations not only from the upper lobe to the base, but also from the right lower to the right upper, and from the left lower to the right upper lobe when the patient assumed the proper posture to permit spilling in these directions.

Should the patient's original position be reassumed after the migration has taken place, the secretions can return to their former position, reobstruct the bronchial openings and produce a recurrence of the atelectasis.

Occasionally infection plays a rôle in these recurrences. Highly virulent aspirated material causes an inflammatory edema of the bronchial opening where it lodges; and although a postural change

may permit the evacuation of the pus and a temporary disappearance of the atelectasis, the continuance of the infection and the increase in the localized bronchial edema lead to a later occlusion of the same bronchus and a reëstablishment of the atelectasis at the original site. There are no just grounds for classifying this edema on an angioneurotic basis; and we cannot agree with those who believe that angioneurotic edema is a factor in the usual type of postoperative atelectasis.

Sante Maneuver and Spontaneous Cures. The occasional spontaneous cures without treatment and the success of the Sante maneuver are dependent on this same principle of internal drainage which permits secretions to spill away from the occluded bronchus and allows air to enter the previously involved lung. As has been pointed out, it is not necessary to expectorate this material in order to get relief, but as long as complete expectoration does not take place, there is always the danger of a recurrence or migration.

Influence of Anesthetic Agent. When it is remembered that aspiration can take place in the unanesthetized as well as in the anesthetized, it is not surprising that postoperative atelectasis occurs following all types of anesthesia. The facilities offered for aspiration and the inability to expectorate play the more important rôle, but the postoperative duration of the narcosis is also important; and for these reasons, we should avoid those anesthetics which leave the patient irrational, uncoöperative and unable to expectorate for hours after his return to the ward.

Prevention and Treatment. Success in the management of these cases depends upon the strictest attention to detail not only during the operation but also before and afterward. Therefore, measures should be instituted to decrease the amount and virulence of the mouth secretions, to prevent aspiration, and to maintain the normal air flow to the lung.

Terry[15] has shown clearly that both the incidence and seriousness of postoperative pulmonary complications could be lessened decidedly merely by the treatment of faulty mouth hygiene in general surgical cases during the 12 hours preceding the operation.

The preliminary management of general surgical cases is altered somewhat when there is an associated pulmonary disease such as chronic bronchitis, asthma, bronchiectasis, pulmonary tuberculosis or pulmonary abscess. In such cases, apart from the nature of the surgical procedure, it is advisable to treat the patient bronchoscopically before the operation so as to empty the bronchi and prevent the spilling of pus and secretion throughout the lung. Otherwise, it will be almost impossible to escape the spread of the pulmonary disease and the obstruction of the bronchi leading to previously uninvolved areas. The bronchoscopy can be performed under local anesthesia in from 1 to 3 minutes and under such circumstances it is not a trying procedure for the patient. Whenever

thoracoplasties, paraffin fillings, or pulmonary cautery operations are contemplated, the emptying of the bronchi is absolutely indicated; because during the chest operation, pus is squeezed out of the diseased area and if this is not expectorated or mechanically removed, a postoperative pulmonary complication will be almost inevitable. It is such a mechanism that explains the spread of tuberculosis to the base of the same lung or into the contralateral side following thoracoplastic operations. As discussed in a previous paper,[16] many of these factors play a prominent rôle in the cause of death following operations upon the lung.

The posture of the patient during and following the operation is very important. It should be such as to prevent the drainage of material into the bronchi. In general, the Trendelenburg position is to be recommended; and the erect or semi-Fowler posture is to be reserved for the exceptional case. The Fowler position should be prohibited also in patients who are vomiting or undergoing gastric lavage, for these are the occasions at which aspiration can take place most readily.

General anesthesia is not contraindicated if it is so given that the patient awakens immediately following the completion of the operation. Scopolamin and morphin (twilight anesthesia), amytal and avertin do not fall into the approved list of anesthetics, because the postoperative period of narcosis is so long that it interferes with the expectoration of the aspirated intrabronchial secretions. For thoracoplastic operations, the anesthesia employed by Ziegler is ideal. He dispenses with all preliminary narcotics and sedatives and uses local throughout the entire operation. This permits expectoration at all times. Graveson employs a very light ether anesthesia along with local; but he insists on the patient expectorating thoroughly before leaving the operating table. The low incidence of the postoperative spread of pulmonary disease in his cases speaks well for this method.

We must now consider the occasional patient who develops severe respiratory difficulty on the operating table at a time when the anesthesia is so deep that expectoration is impossible and when the removal of mouth secretions fails to give relief. For the past 5 years, we have made bronchoscopy a routine procedure in such instances and have had very gratifying results. Our first patient of this type developed difficult breathing and very loud rhonchi just before the completion of a hysterectomy under ether anesthesia, and it seemed almost certain that a postoperative pulmonary complication would ensue. The bronchoscope was employed at once; and thick mucoid material was found in and removed from the pharynx and trachea. The respiratory difficulty was relieved immediately and the patient made a strikingly uneventful convalescence. In a second patient whose condition was less alarming but in whom very definite rhonchi were present, considerable viscid

material was expectorated following the postoperative employment of the Trendelenberg position. This patient's convalescence was similarly uneventful. The decision as to whether the bronchoscope or postural drainage is to be used in the individual case must rest upon the judgment of the surgeon and the facilities at hand; but in urgent cases, bronchoscopy offers the quickest and surest means of relief. In both of the above cases, the secretions which were removed from the bronchi were the same as those which are seen so often in the mouth of anesthetized patients. This should sufficiently emphasize the importance of keeping the mouth and pharynx free of excess saliva if aspiration and postoperative pulmonary complications are to be prevented.

Much has been written concerning the danger of using atropin if atelectasis is to be prevented; but we have found no contraindication to its pre-operative use if the bronchi are free of exudate, because by diminishing the amount of secretion, the opportunities for aspiration are minimized. We do not use it before lung operations, however, nor after the rhonchi appear, because rational treatment demands the removal and not the thickening of the intrabronchial secretions. Postoperatively, we look with disfavor upon atropin but prefer the administration of expectorants.

Pure carbon dioxid inhalation has proved of value both in the prevention and treatment of postoperative pulmonary complications, because it causes hyperventilation and deetherizes the patient. The inhalations are given on the operating table in the Trendelenburg position at the end of the operation and are repeated 3 or 4 times daily for the first 2 days postoperatively. The amount of gas given should be sufficient to stimulate deep rapid breathing but it should not be carried on to the point of fatigue. What has been said previously concerning posture applies equally well during the carbon dioxid inhalations, for the aim should be to allow the secretion to drain out of and not deeper into the bronchi. We warn again against the general use of the semi-Fowler position; this hinders adequate drainage and increases the seriousness of the patient's condition. Correct posture depends on the site of the atelectasis and is determined on anatomical grounds in keeping with the principles of internal drainage.

For general use postoperatively, we can recommend Sante's method of rolling the patient from side to side; but patients that do not respond to these measures are to be bronchoscoped. This permits the removal of the intrabronchial secretions and the treatment of the edematous bronchial mucous membrane with cocain, adrenalin, ephedrin, or silver nitrate. The efficacy of the bronchoscopic treatments is increased if followed by postural drainage to empty the smaller bronchi that are beyond the reach of the bronchoscopic suction.

Conclusions. 1. The cause and entire clinical picture of postoperative massive collapse of the lung (pulmonary atelectasis) can be explained on a combined mechanical and infectious basis.

2. Postoperative pulmonary atelectasis is due primarily to the bronchial obstruction resulting from the presence of excess intrabronchial secretion and the influence of "internal drainage" upon these secretions.

3. By "internal drainage" is meant the spilling of material from place to place within the tracheobronchial tree to spread infection, obstruct bronchi and shut off the air flow to a portion of the lung.

4. This spilling depends on the amount and viscosity of the secretion and the posture of the patient.

5. In certain pulmonary diseases, the excess secretions are already present within the tracheobronchial tree before the operation; but in other conditions, the secretions are aspirated from the mouth and nasopharynx during or immediately following the operation.

6. Internal drainage accounts for the varied onset of postoperative pulmonary atelectasis, diversity of symptoms, predilection of sites, extensiveness, migrations, recurrences, and the response to various treatments.

7. We do not believe that vasomotor, phrenic, vagus or sympathetic reflexes, angioneurotic edema or compression of the chest wall are primary etiologic factors in postoperative atelectasis.

8. Careful attention to the mouth hygiene, the posture of the patient during and following the operation, the prevention of aspiration and the removal of intrabronchial secretions should either prevent atelectasis and other postoperative pulmonary complications or decidedly lessen the frequency of their occurrence.

9. Postural exercises, carbon dioxid inhalations and bronchoscopic treatments have proved of value in the management of patients with postoperative atelectasis when carried out in accordance with the principles of internal drainage.

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AN ANALYSIS OF 312 CASES OF DIABETES TREATED IN AN OPEN HOSPITAL IN EIGHT YEARS.

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This report is based on a review of all the diabetic patients treated at the Lancaster General Hospital during the first 8 years during which insulin was available for general use. The Lancaster General Hospital (265 beds) is "open" to all physicians of the county, and each physician is permitted to treat his own private patient. The 312 cases reported were treated by 47 different medical men. Although the majority of the patients were under the care of a few physicians, a considerable number of patients were treated by physicians who see only a relatively few cases of serious diabetes and whose experience in this field was consequently limited. There is a natural tendency for medical literature to contain many more reports of successful therapy than of unsatisfactory therapy, but we felt that, especially in diabetes, there were just as many lessons to be learned from the errors of treatment as from the successes. Consequently we have freely discussed both.

In the 8 years a total of 312 cases were treated, of whom 43 (13.7 per cent) died before leaving the hospital (Table 1). There were 194 females and 118 males. The total cases were separated into: (1) Surgical, those who had some form of operation, not including extraction of teeth; and (2) medical, including all the unoperated cases.

There were 59 operative cases, with 9 deaths, a mortality of 15.2 per cent. During the 8 years 19 per cent of all the patients admitted with diabetes underwent some surgical procedure. The reasons for operation and causes of death are listed in Table 2.

TABLE 1.—ANALYSIS OF CASES.

Year	Total No. patients.	No. of operations.	Percentage of operations.	No. of deaths.			Av. No. days surgical cases in hospital.	Av. No. days medical cases in hospital.
				Med.	Surg.	Total.		
1923 to 1924	36	6	16.7	3	2	5	36	19
1924 to 1925	36	6	16.7	5	2	7	27	24
1925 to 1926	38	7	18.4	5	0	5	19	14
1926 to 1927	45	11	24.4	5	0	5	27	10
1927 to 1928	28	3	10.7	6	1	7	20	10
1928 to 1929	32	7	21.9	2	0	2	29	43
1929 to 1930	31	2	6.5	2	0	2	15	20
1930 to 1931	66	17	25.8	6	4	10	32	15
Totals for 8 years	312	59	18.9	34	9	43	26	19

TABLE 2.—SURGICAL CASES—LIST OF OPERATIONS.

Operation.	No. of cases.	No. of deaths in hospital.
Amputation of one or more toes	3	
Amputation through foot	1	
Amputation of leg	13	3
Amputation of thigh	5	1
Amputation of fingers	1	
Bone curettage	1	
Open reduction—fracture of patella	1	
Cataract extraction	2	
Tonsillectomy	4	
Thyroidectomy	2	
Laparotomy (exploratory)	1	
Cholecystectomy	3	1
Appendectomy	1	
Hysterectomy	3	2
Suprapubic cystotomy	1	
Cervical polyp excised	2	
Abscesses incised	6	
Carbuncles	6	
Abscess of liver	1	1
Amputation of breast	1	
Colostomy	1	1
Total for 8 years	59	9

In the 253 medical cases there were 34 deaths (13.5 per cent mortality). The medical complications are listed in Table 3. Under the classification of coma are included only those cases which were apparently primary diabetic coma, *i. e.*, not secondary to some other disease or infection, such as pneumonia, septicemia, etc. The number of cases on this list is rather large because in most of these cases autopsies were not permitted. We believe that if all these cases had been autopsied the number under this classification would be much smaller, due to the discovery of various unexpected lesions, such as abscesses of the kidney and the like.

Turning to the amount of insulin used in treatment (Table 4), we found that the surgical cases during their stay in the hospital

took approximately the same amount as the nonsurgical cases, but on discharge the insulin dosage of the surgical cases was a little higher than the medical, probably due to the temporarily decreased sugar tolerance caused by the condition operated upon—frequently an infection. In comparing the dosages of insulin in the first year of this series with that of the last year, one notes the striking increase in amount of insulin per patient. However, this marked difference, on closer inspection, is seen to exist merely between the first year and the latter 7. It is due undoubtedly to early timidity in using the larger doses.

TABLE 3.—MEDICAL COMPLICATIONS.*

Complications.	No. of cases.	No of deaths in hospital.
Coma (without surgical complications)	27	22
Infection—toes	17	
Infection—foot	7	1
Acute bronchitis	1	
Pleurisy	1	
Pneumonia	3	1
Pulmonary tuberculosis	2	
Carbuncle	3	1
Cystitis	1	
Septicemia	2	2
Otitis media	2	
Corneal ulcer	1	
Syphilis	2	
Arthritis	1	
Catarrhal jaundice	1	
Acute cholecystitis	1	
Chronic cholangitis	1	
Cholelithiasis	1	
Nephritis	4	1
Cerebral hemorrhage or embolism	5	5
Fracture of femur	1	
Compound fracture of fibula	1	
Dry gangrene—lower extremity	3	
Toxic thyroid	1	
Hypothyroidism	1	
Hypoglycemia	2	
Alcoholism	2	
Hemochromatosis	1	
Ruptured appendix	1	1
Total for 8 years	96	34

* If more than one complication existed in the same patient, only the most important one is listed.

TABLE 4.—MAXIMUM DAILY DOSAGES OF INSULIN.

Year.	Average of surgical cases, units.	Average of medical cases, units.	Average of total cases, units.
1923 to 1924	20	18	19
1924 to 1925	44	33	38
1925 to 1926	54	35	45
1926 to 1927	39	43	41
1927 to 1928	48	46	47
1928 to 1929	35	40	38
1929 to 1930	26	48	37
1930 to 1931	45	72	59

TABLE 5.—DAILY INSULIN DOSAGE ON DISCHARGE.

Year.	Average of surgical cases, units.	Average of medical cases, units.	Average of total cases, units.
1923 to 1924	7	13	10
1924 to 1925	27	25	26
1925 to 1926	41	24	32
1926 to 1927	27	22	24
1927 to 1928	32	18	25
1928 to 1929	6	17	12
1929 to 1930	22	28	25
1930 to 1931	30	25	27

As would be expected, the average hospitalization of the surgical cases was longer than that for the medical (Table 1). For the 8 years surgical patients averaged 26 days in the hospital and medical, 19 days.

Uniformly Good Results in All Mild Cases. The moderate and mild cases of diabetes obtained uniformly good results. The only requirement was that the diet be somewhat restricted in carbohydrate although containing sufficient calories. Insulin was used frequently in small doses but occasionally was not necessary. Corresponding to the general trend in most diabetic clinics, the treatment in this hospital has swung from the starvation type of diet, with a minimum of insulin, to the free carbohydrate, more normal diet with free use of insulin if necessary. There are a number of advantages for this higher carbohydrate and higher total caloric allowance:

1. It is closer to the normal diet of the healthy person.
2. It permits keeping the patient at a normal weight and in perfect strength.
3. Since the patient is well nourished there is less temptation for "cheating" in the diet.
4. Finally, it is believed by some that the complete oxidation of fats, brought about by the abundant carbohydrate oxidation, lessens the likelihood of vascular sclerosis.

The disadvantages of this method are:

1. The greater expense of treatment due to the larger doses of insulin.
2. A certain number of patients, who otherwise could do without the injections, when on a high carbohydrate diet must be inconvenienced by taking insulin.
3. There is considerably more danger that patients on the high diet and high insulin régime may become careless and neglect the insulin suddenly—occasionally resulting in acidosis. For example, 2 of our cases after short periods of neglect of diet and insulin were admitted to the hospital in coma and died.
4. Hypoglycemic reactions (insulin shocks) are more common.
5. A serious objection is that, unless carefully controlled, the diabetic patient on liberal diet and insulin is liable to get fat—a dangerous thing in severe diabetes.

However, the experienced diabetic patient taking insulin soon

finds out that he can eat satisfying quantities of food by slightly increasing his insulin and physicians must always adapt their treatment to the conditions of the individual case.

Severe Cases, Comatose and Precomatose. In contrast to the uniformly good results obtained in all the mild cases of diabetes, the results in coma or precomatose patients in an open hospital were not so satisfactory. In the hands of those physicians particularly interested in diabetes, comatose patients were treated energetically by gastric lavage, enema, external heat, fluids by hypodermoclysis (or intravenously if patients were unable to swallow) and sufficient doses of insulin and glucose carefully controlled by urinary and blood sugar estimations and tests for acidosis. However, there is considerable room for improvement in the treatment of coma by the physician or surgeon who sees only an occasional case and does not appreciate the gravity of the condition.

Staff Coöperation for Adequate Treatment of Severe Diabetes. Because of inability to concentrate the treatment of diabetes under one service or under a diabetic team due to the very nature of an open hospital, our attempts to improve results have been directed mainly toward the further education of all physicians using the hospital in the proper management of diabetic coma. This is done mainly by a free discussion of cases at staff meetings. The results in improvement of treatment are gratifying. Another tendency which also develops with further education is that, although the mild diabetic is treated by everyone, the coma cases are more liable to be referred to those physicians who are known to treat considerable numbers of diabetic patients and who, therefore, are presumably more competent to treat the emergency of coma.

Because of the fact that patients will often delay all day and take decisive steps only toward nightfall in serious diabetes, it is frequently necessary to apply the first and most energetic diabetic treatment at night. It then becomes necessary not only for the staff physician to remain on duty all night, but he must have the coöperation of a trained laboratory worker. Usually the resident physician on laboratory service has been used at this Hospital. One of the regular laboratory technicians is also on call at night for such emergencies. The staff physician should intimately supervise and personally see the patient in coma at frequent intervals during the first 24 hours at least. The practice of some physicians to turn over patients in diabetics coma to the intern who is possibly theoretically well grounded, but often has had no practical experience with such cases, is certainly to be deplored.

The Treatment of Acidosis Is of Primary Importance. The elimination of acidosis is the first principle in the treatment of diabetic coma. Five medical cases suffering from various complications and 1 postoperative case were rescued from deep coma. The relatively small number of coma recoveries is partially due to the fact that in this series a diagnosis of coma was not made unless the

patient was entirely unconscious and could not be aroused. It is probably better usage to include in this group those patients who are merely drowsy or mentally sluggish and show large amounts of ketone bodies in the urine and a marked lowering of the plasma CO_2. We have found instances of diabetic patients who were subjected to major operations without any estimations for the presence of acidosis. In all surgical cases the determination of the presence or absence of acidosis should be a routine procedure, not only before but also after operation. In some cases in this series, although the presence of acidosis had been definitely established by clinical and laboratory examinations, it was disregarded and attention concentrated on simply maintaining the blood sugar at a normal level—with disastrous results. One case of coma had a normal blood sugar level but laboratory tests showed marked ketosis at the time of death. Postmortem examination was negative, indicating that diabetic coma was the deciding factor. The condition which demands first attention is not the height of the blood sugar, but the state of acidosis as determined clinically by drowsiness, dry skin and mucous membranes, sweet odor of the breath, etc., and by the laboratory tests for acetone and diacetic acid in the urine and CO_2 in the blood and alveolar air. "Fats burn in the flame of the carbohydrate." The burning of carbohydrate is accelerated by insulin. Therefore, if the blood sugar is high, large doses of insulin may be safely employed to burn carbohydrate and consequently indirectly burn fatty acids. If the blood sugar approaches normal acidosis still persists, glucose must be supplied by mouth, intravenously or otherwise in order to provide an additional fuel for the burning of the rest of the fatty acids.

Insulin. Regarding the frequency of administration and total doses of insulin necessary there was tremendous variability. Depending on the difficulty in eliminating the acidosis, patients in coma received doses of from 20 units every 2 or 3 hours to 40 units every 15 minutes. One boy of 12 years required 360 units of insulin the first 24 hours to clear up the coma and was discharged in 36 days, taking no insulin whatever. A girl, aged 7 years, with measles and bronchopneumonia, required 750 units the first 24 hours and eventually recovered. A Hebrew patient, aged 65 years, with severe and extensive infection of the foot, required 100 units of insulin 3 times daily for a period of 4 days (April 28 to May 1, 1930), and he was not even in coma. Squibb's and Lilly's insulin were interchanged in this case and samples of the insulin used were sent to the Lilly Laboratory and potency verified at the time these doses were used. The fatal case of septicemia with bilateral renal abscesses received 1000 units of insulin in 6 hours, with practically no effect on the blood sugar.

Danger of Hypoglycemia in Diabetic Coma. If the blood sugar is brought too low (hypoglycemia) a very real danger is introduced. When coma cases are treated too energetically with insulin or by

large doses of insulin insufficiently checked by urinary and blood sugar estimations, a diabetic patient in coma may have hypoglycemia superadded to his primary disease and die without having had any lucid interval. It would seem probable that this happened in a comatose patient admitted with a blood sugar of 440 mg. per cent. Massive doses of insulin reduced the blood sugar to 30 mg. per cent and the patient died without having recovered consciousness. Unfortunately an autopsy was not obtained. Diabetic patients can sometimes live for days in comparative comfort with blood sugar level between 300 and 400, but when the blood sugar is reduced to 30 or 40 mg., unless glucose is promptly administered, survival is probably only a matter of hours.

Administration of Fluids in Coma. In the treatment of coma one must be certain that the fluids administered actually get into the body of the patient. One of the cases in the series exemplifies what may happen when this is not accomplished.

Case Abstract. CASE 1.—The patient was a girl, aged 13 years, known to have been diabetic for 7 months. Two days before admission she had headache and was drowsy. She was admitted to the hospital in coma at 10 P.M. During the next 4 hours she received 80 units of insulin and was given glucose solution by proctoclysis. At 2 A.M. the nurse's record states: "Patient vomited a large amount of dark green liquid and expelled the glucose solution from the bowel." At 2.10 A.M. she died.

Although an autopsy was not obtained, we may assume that part of the failure in treatment was due to the fact that although the patient was seriously dehydrated, the stomach and colon were distended by fluid which was not being absorbed. To insure effective action, the fluid should have been given in this case by hypodermoclysis or intravenously.

Importance of Infections. Every diabetic patient should be warned that any infection or, in fact, any condition which upsets the even tenor of his daily life should make him all the more careful of his diabetic regulations and visit his physician for even minor affections when in doubt. A common cold or hoarseness may be a signal of reduced sugar tolerance. Two cases will illustrate the more serious infections.

CASE 2.—A female patient, aged 56 years, was admitted in coma with a history of increasing drowsiness for the 2 days preceding admission. Her blood sugar was 516 mg., blood plasma CO_2 17 volumes per cent and the blood urea nitrogen 28 mg. She was given the usual recognized treatment for coma plus very large doses of insulin. Two hours after admission the blood sugar was 410 mg. She received 1000 cc. of normal saline by hypodermoclysis and 100 gm. of glucose in 1200 cc. of water intravenously during the 6 hours of treatment. Intravenously and intramuscularly, a total of 1000 units of insulin were administered during the 6 hours in the hospital but she died with a blood sugar at 520 mg. Autopsy disclosed a carbuncle of one kidney and scattered abscesses throughout the other. The colon bacillus was isolated on culture.

CASE 3.—Another patient, a female, aged 48 years, was admitted with a carbuncle on the lip. In spite of the fact that the blood sugar was persistently kept normal and acidosis was successfully combated, the patient died. Autopsy showed metastatic abscesses of the lungs and kidneys.

Both the preceding cases emphasize the importance of obtaining postmortem examinations in diabetic patients so that we "do not lose faith in insulin." In the first case the renal abscesses were entirely unsuspected antemortem and the case apparently was one in which insulin simply had no effect.

In the patients who suddenly developed diabetic acidosis without having had previous knowledge of a diabetic tendency there was usually found some severe precipitating infection, such as septicemia, pneumonia, carbuncle, etc. Conversely, when diabetic acidosis develops suddenly in a patient who has previously not been diabetic the prognosis must be more guarded than if the acidosis developed in a recognized diabetic patient. In the first-mentioned type of case a very diligent search for infection should always be made.

Although much larger doses of insulin are required when infections are present, the diabetic patient should not succumb to any infection which could be cured in his nondiabetic brother. The recovery of the 2 cases of pneumonia and the numerous severe peripheral infections are illustrative of the good results which are possible. In order to obtain the best results, all diabetic patients with severe infections must be hospitalized.

Hypoglycemia. Although diabetics with infections may require large doses of insulin, other patients may be thrown into hypoglycemia by apparently insignificant doses of insulin.

CASE 4.—An adult female, who had been receiving 10 units of insulin daily, one afternoon became very weak, perspired profusely and became stuporous. Ten teaspoonfuls of sugar in 4 ounces of orange juice and 5 minims of adrenalin were administered, but her condition became progressively worse. One and a half hours later it was necessary to give 20 cc. of 50 per cent glucose intravenously. The patient recovered.

Two cases were admitted to the hospital in hypoglycemic coma, "insulin reaction." Both occurred in 1930–1931 and both recovered. The notes on 1 case are interesting:

CASE 5.—The patient was a female, aged 35 years, who was comatose on admission, but blood sugar proved to be 25 mg. per 100 cc. She had been treated at the hospital 5 months previously for diabetic coma and at the time of discharge was taking insulin, 20 units, 3 times daily. It was learned that just previous to the present admission she had been very irregular in her diet and on the day of admission, although she had not felt well before dinner, she had taken the usual amount of insulin and eaten very little. She became unconscious soon afterward. This case illustrates both the danger of carelessness in diet and the importance of reducing the insulin dosage if little or no food is taken at a meal.

The importance of guarding against hypoglycemia in diabetic coma has already been mentioned.

Importance of the Adherence to Diet and Insulin. As other observers have already pointed out, we found that most of our cases of uncomplicated coma were due to negligence. Many of the patients who died in diabetic coma had been rescued from coma one or more

times previously. The 3 following cases illustrate the penalty of laxity on the part of the patient.

CASE 6.—A female, aged 20 years, had been known to have diabetes for 3 years. She had been negligent of the diet the last few days before admission and had stopped the use of insulin. The day before admission she was taken ill with nausea and vomiting. She died 36 hours after admission, although she received 510 units of insulin in the first 24 hours.

CASE 7.—Another patient was a male, aged 38 years. The resident physician's notes state: "Patient knew he had diabetes for 3 years. He was admitted to the hospital previously and put on diet and insulin. He kept to the diet fairly well and took insulin while at home. When away from home he was careless about the diet and insulin. Last week he was away and omitted insulin. When he returned he felt badly but refused insulin. On the morning of admission he was irrational." He died within 24 hours.

CASE 8.—The third case was a male, aged 58 years. Diabetes had been diagnosed 2 years previously. One year before final admission he was treated for carbuncle. The notes state: "He had a special diet to which he had not adhered recently. Had gone to an 'electrical doctor' who told him he had cured his diabetes and that he should eat bread and potatoes. He was well until 2 days ago." He died in coma.

Surgery in Diabetes. One should never underestimate the risk in operating upon a diabetic patient. One patient had a leg amputation for gangrene and did not even require any insulin; another had an uncomplicated tonsillectomy and was comatose for 4 days before recovery; a third patient underwent thyroidectomy and was discharged on the fourteenth day with attention to diet alone and without having required any insulin.

It is especially important to control acidosis after surgery rigidly. Probably, if the acidosis could have been controlled following a leg amputation in 1 of our patients, the secondary thigh amputation would not have been required.

Another point of great importance in surgery, especially of the lower extremities, is the exact differential diagnosis between inflammation and necrosis or actual gangrene. Inflammatory cases, even if extensive, can frequently be saved by vigorous diabetic treatment plus incision and drainage without amputation. For example, a patient recovered from a very severe infection involving the whole left foot and ankle. On a diagnosis of gangrene the leg would certainly have been removed. However, in cases where there is massive dry gangrene from complete occlusion of the bloodvessels, the only possible curative treatment is amputation. Yet conservative treatment, even of the dry gangrenous areas, will often yield good results. Occasionally even the large black gangrenous areas on the feet are superficial and long-continued conservative treatment will eliminate the slough and preserve the leg.

The following case is given in more detail both because of the difficulty in diagnosing between intestinal obstruction in appendiceal peritonitis and the vomiting of the precomatose diabetic, and to illustrate a possible danger in the treatment of diabetes after operation.

CASE 9.—A female patient, aged 41 years, was admitted to the hospital after having had abdominal pain for 4 days. She was immediately operated upon and an acutely inflamed appendix removed. It was noted that there was considerable peritoneal exudate at the time of operation and a cigarette drain was inserted in the pelvis. Because of the danger of spreading the peritonitis the abdomen was not explored, although it was remarked that there was considerable distention. After operation sugar was found in the urine. She was not known to have had diabetes previously, although her father had died from diabetes.

For 3 days after operation she did fairly well. On the fourth day she began to vomit brownish liquid with an odor slightly suggestive of feces, became increasingly restless (not drowsy), the abdomen became still more distended and her temperature rose to 104° F. Her blood sugar was 320, urine sugar ++++, acetone + and diacetic acid ++.

No liquids were permitted by mouth but a tube was inserted into the duodenum and about 2400 cc. of thin brownish fluid were drained out through the tube in 10 hours. During this time she was given 1000 cc. of 10 per cent glucose intravenously in divided doses. On the fourth day following operation she received 260 units of insulin in doses varying from 10 to 40 units each. The blood sugar dropped from 290 to 98, the patient was not quite so restless, did not complain of so much abdominal distress and the distention was somewhat less. The duodenal tube was removed and the patient encouraged to take liquid by mouth, which she did very freely, about 3000 cc., without apparent discomfort.

Following the use of the intravenous glucose the urine had contained sugar, 2+ to 4+ amounts, at the 2-hour examinations. At this time the blood sugar was 98, blood urea nitrogen 28 and blood CO_2 48 volumes per cent. The patient said she was comfortable, but her skin was cold and clammy. About 7 hours later the patient suddenly went into collapse, the temperature rose again to 104°, the pulse to 120 and the skin felt cold and wet. She vomited a little brownish liquid and became quite restless, partially delirious. The duodenal tube was reinserted, against her strenuous vocal objections, although she was too weak to oppose it physically. In spite of draining off about 1 quart of brownish liquid, her condition progressed and she died, less than 45 minutes after protesting against the insertion of the tube.

Autopsy showed that the small bowel was greatly distended by liquid and occupied most of the abdominal cavity. There was slight dilatation of the stomach. There was a moderate degree of generalized peritonitis. About 8 inches proximal to the cecum was an S-shaped kink in the ileum caused by recent inflammatory adhesions which were apparently strong enough to obstruct the lumen, because the distal 8 inches of the ileum were of normal caliber and contained very little fluid. The large bowel was normal. The pancreas, liver, kidneys and spleen were normal to inspection and palpation. The urinary bladder contained about ½ ounce of urine.

Discussion of Case 9. If the diagnosis of intestinal obstruction could have been made during the first 3 days and before the patient went into shock, the obstruction might have been relieved even at the expense of further spread of the peritonitis. Vomiting and abdominal pain are also symptoms of developing acidosis and coma, but severe acidosis was negated in this case by the almost normal blood CO_2 and very slight amount of acetone in the urine as well as by the restlessness and mental alertness of the patient (the opposite of coma drowsiness). After the patient survived the first shock and collapse large quantities of liquid were permitted by

mouth to further prevent the danger of acidosis. This large amount of liquid evidently hastened the end because the small intestines were greatly dilated postmortem. That she did not die in diabetic coma is shown by the absence of severe ketosis and the fact that up to within 45 minutes of her death she was restless and talked constantly. We believed that the moderate generalized peritonitis may have weakened the strength of the small intestinal muscular wall (a form of paralytic ileus) so that it could not force the intestinal contents past the relatively weak adhesions caused by a localized peritonitis of only a few days' standing.

Summary. An analysis of 312 consecutive cases of diabetes is presented. These patients were treated in an "open hospital" by 47 different physicians over a period of 8 years, with a total hospital mortality of 13.7 per cent. In the 59 surgical cases the mortality was 15.2 per cent and in the 253 medical cases there was a mortality of 13.5 per cent.

Although no difficulty whatever is experienced in the control of so-called "mild diabetes," under these conditions the utmost care and diligence is required for success with severe comatose or precomatose patients. The condition which calls most urgently for treatment in severe medical, as well as pre-operative and postoperative surgical cases, is the acidosis. Until the acidosis is successfully combated the height of the blood sugar and the glycosuria are of concern mainly as guides in the prevention of hypoglycemia from over dosage with insulin. After the acidosis has been controlled, the blood sugar can be finally standardized and the final traces of sugar removed from the urine by adjustment of diet and insulin.

ACUTE HEMORRHAGIC NECROSIS OF THE PANCREAS.

(A CLINICO-PATHOLOGIC STUDY WITH A NEW CLASSIFICATION BASED ON ETIOLOGY.)

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A SIMPLE classification of acute hemorrhagic necrosis of the pancreas is herewith presented, permitting etiology to determine the groups; it is believed that the pathogenesis in each group can

be established. The classification is based almost entirely upon observations made in our laboratory. It is not our intention to discuss the massive literature that has accumulated on this subject, except to mention that attention has been too strongly focused on the inflammatory group, the so-called "acute hemorrhagic pancreatitis" and that other groups, equally clear-cut, have been dismissed under such terms as "agonal or postmortem autodigestion."*

Pancreatic necrosis is not a disease entity; it is a reflection in the pancreas of disease process elsewhere. The nature of the reaction within the pancreas varies with the nature of the causative factor and presents a more or less characteristic gross and histopathologic picture; certain clinical features are sufficiently constant to bear out these etiologic and pathologic groups. Thus it is felt that the following classification of "acute hemorrhagic necrosis of the pancreas" is necessary:

I. Inflammatory.

(*a*) Dependent on infection and/or obstruction of the biliary tract.

(*b*) Dependent on infection from contiguous structures.

II. Degenerative.

(*a*) Dependent on cardiovascular disease.

1. Congestive heart failure type.
2. Hypertensive arteriosclerotic type (pancreatic apoplexy).
3. Embolic type.

(*b*) Dependent on general toxic phenomena.

(*c*) Dependent on trauma to the pancreas.

We have observed a large number of cases; of these, 30 were selected for detailed etiologic, clinical and pathologic analysis, and on this latter group the majority of the data recorded herein depends.

I. Inflammatory. (*a*) DEPENDENT ON INFECTION AND/OR OBSTRUCTION OF THE BILIARY TRACT. This, the least common of all, is the abdominal calamity recognized by the surgeon as "acute hemorrhagic pancreatitis." In the words of Moynihan, "the suddenness of its onset, the illimitable agony which accompanies it and the mortality attendant upon it, all render it the most formidable of catastrophes." Coming on usually after a good meal, excruciating epigastric pain occurs, frequently referred to the midback and loins; the patient goes rapidly into collapse, lividity of the face and sometimes patchy cyanosis over torso and extremities being notable. Exquisite abdominal tenderness is elicited, especially in the epigastrium, but rigidity is not in proportion. This is the type of case that at operation presents to the surgeon extensive fat necrosis, an acrid, serosanguinous, intraperitoneal exudate and a large, firm, edematous, red-black, friable pancreas lying at the bloody, semi-

* For complete consideration of the pathologic anatomy of the subject see Gruber; for the pancreas in heart disease see von Glahn and Chobot, Gerlei, and Schweizer.

destroyed base of the mesentery. This form has been in the past rather artificially divided into three types, *viz.*, hemorrhagic, gangrenous and suppurative, the difference, however, being only a matter of degree and duration, the essential nature identical. These cases almost uniformly give a history of previous recurring attacks of epigastric pain, nausea and vomiting of varying severity.

The etiologic agent is unquestionably a diseased biliary tract, as result of infection, small calculi or both. Many pathologists are disturbed on finding the bile passages entirely patent at necropsy examination and even the gall bladder free of stones. It is perfectly conceivable, however, that a small calculus, sufficient to cause temporary obstruction at the ampulla of Vater and reflux of infected bile into the main pancreatic duct, might be dislodged through vomiting and retching by the time the patient has reached the necropsy table.

A predisposing factor lies in the anatomic relation of the main and accessory pancreatic ducts, the variations of which have recently been described by Simkins. Moynihan feels that the two factors essential in the development of the condition are: (1) An anatomic arrangement of the parts at the termination of the two ducts which permits of their conversion into one channel by closure of the orifice of the ampulla into the duodenum, and (2) the presence of infected bile, associated or not with cholelithiasis in the gall bladder or in the bile ducts.

Reflux of duodenal contents into the pancreatic ducts is practically impossible. We attempted to produce this in the cadaver by ligating the duodenum below the ampulla, injecting colored substance into its lumen, and exerting extreme pressure. No coloring matter appeared within the pancreas, not even within the common bile duct. It has been said that an increase of intraduodenal pressure to 1000 mm. of water does not overcome the resistance of the ducts. Thus we believe that the anatomic arrangement and physical conditions existing in the body preclude this as an etiologic factor.

The cause of the actual necrosis is the presence of activated pancreatic juice within the substance of the gland. The activation of trypsinogen is accomplished normally by enterokinase of the duodenum, but we have shown that duodenal contents do not enter the pancreas. This activation, however, is accomplished by destructive bacterial action on the pancreatic cells, freeing the proteolytic enzymes therein. Pancreatic lipase needs an alkaline medium *and* bile for its activation. Since bile here enters the pancreas, as we believe, fat necrosis is a prominent feature of this group.

Pathologic Anatomy. The gross picture of the pancreas has already been mentioned. Histologically, evidences of the inflammatory character of this group are prominent; purulent exudate is seen in the ducts and often in the perilobular interstices. Wide-

spread necrosis of the parenchyma occurs, most prominent in the head and body, the tail being involved last. Hemorrhage is occasioned through necrosis of vessel walls by pancreatic ferments. Necrosis of fat is prominent in and about the gland. Late, no structure is recognizable; even the blood undergoes dissolution.

Of the other viscera the gall bladder and liver show the greatest variation from normal. The former organ is usually the seat of low-grade calculous cholecystitis and contains stones, more commonly of the fine, shot-like variety. The liver has, in many cases, undergone fatty metamorphosis and histologic examination shows the periportal region to be the seat of subacute to subchronic inflammation. Evidence of "shock," namely, extreme dilatation of capillary beds, is seen throughout the body.

(*b*) Dependent on Infection From Contiguous Structures. This is mentioned only to be dismissed in as many words, as it does not come within the scope of this paper. It usually follows suppurative peritonitis, portal thrombophlebitis, perirenal abscess (left) and like conditions in which any clinical manifestations emanating from the pancreas *per se* are masked by the symptoms of the major condition. Occasionally, however, chronic perforation of a peptic ulcer will seat itself in the pancreas, giving rise to a subacute pancreatitis which may present puzzling symptoms (such a case is mentioned by Gruber).

II. Degenerative. This second main class is divisible from the preceding one essentially by the difference in the gross and histologic picture of the pancreas, from the lack of evidence of an inflammatory process either in that gland or in the biliary tract and from striking differences in the clinical picture. The basic changes that we are considering are present, namely, necrosis and hemorrhage. Further subdivision of this group on etiologic grounds is made: (1) Those resulting from cardiovascular disease; (2) those associated with a general toxic process.

(*a*) Dependent on Cardiovascular Disease. 1. *Congestive Heart Failure Type.* The cardinal clinical features of cases in this subgroup are those of acute, congestive, right-sided heart failure in which upper abdominal complaints are prominent, especially epigastric pain, nausea and vomiting. The pain often radiates to one or the other hypochondriac regions and to the back, sometimes referred to the precordial region; pain in these cases is usually not severe and is accompanied by marked restlessness. Following the onset of these symptoms, the cardiac collapse becomes more prominent due to the concomitant acute myocardial degeneration, as will be seen later. These severe cases are usually accompanied by elevation of the blood sugar level (often ranging between 200 and 300 mg. per cent). Differentiation from the so-called "liver pain" may be difficult; failure to palpate an enlarged, tender liver and the presence of an elevated blood sugar level should be helpful. Rarely

FIG. 1.—Inflammatory type (dependent on infection of the biliary tract). Suppurative focus in center; duct entirely destroyed. Necrosis is prominent; few acinar remnants persist. (× 90.)

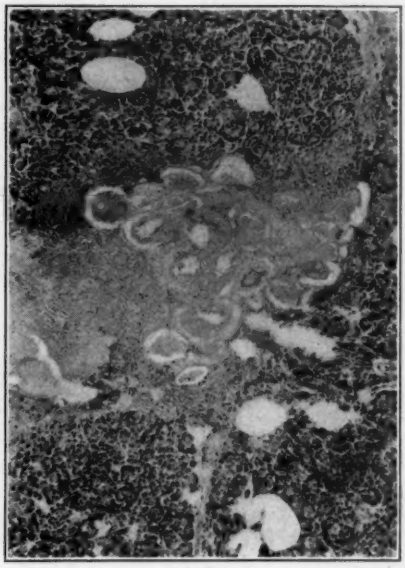


FIG. 2.—Inflammatory type (dependent on obstruction of the biliary tract). Extensive fat necrosis seen in center; reflux of bile prominent in this type case. (× 90.)

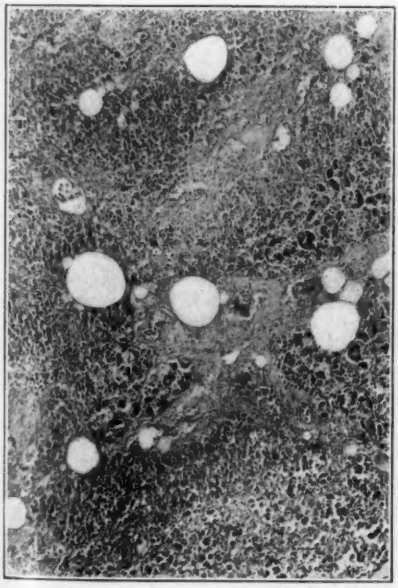


FIG. 3.—Congestive heart failure type. Marked necrosis of pancreatic tissue; but few intact acini remain. Blood semidigested and not visible in photomicrograph. No fat necrosis. (× 82.)

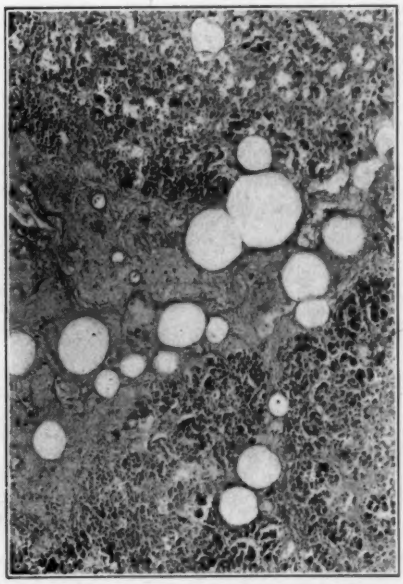


FIG. 4.—Recurrent congestive heart failure type. Majority of pancreatic tissue is necrotic, due to acute cardiac decompensation. In center is a V-shaped scar resulting from a similar previous attack from which the patient recovered. (× 82.)

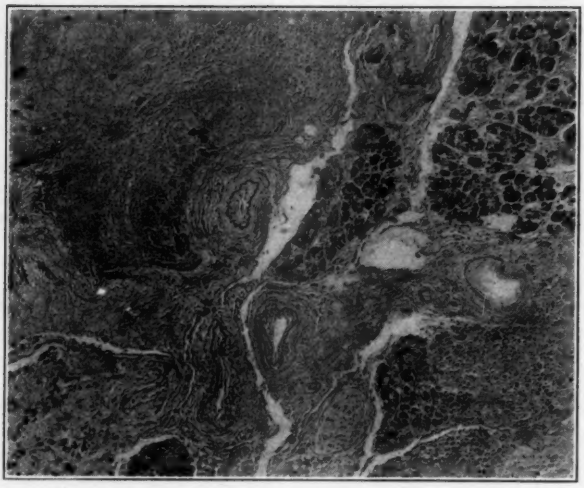
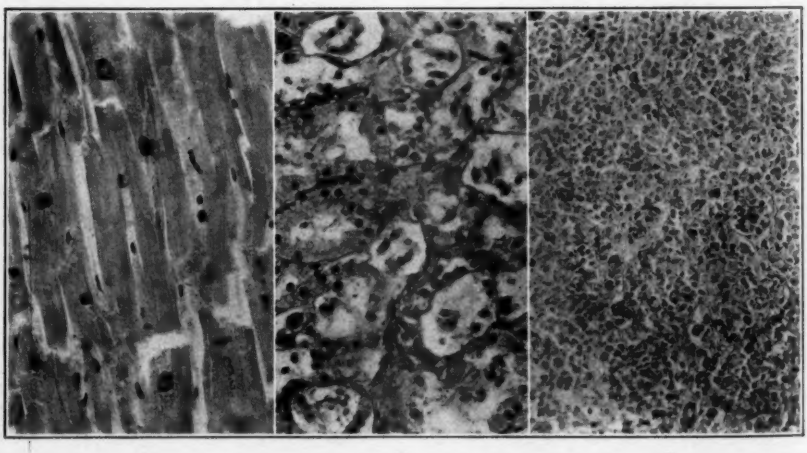


FIG. 5.—Hypertensive arteriosclerotic type. Five markedly sclerotic arteries seen in field, showing prominent internal elastic lamina. Pancreatic tissue preserved in upper right of field; remainder transformed into homogeneous, necrotic, hemorrhagic mass. No fat necrosis. No inflammatory reaction. (× 72.)



A *B* *C*

FIG. 6.—Degenerative type (dependent on general toxic phenomena). *A*, myocardium with extremely swollen and degenerated muscle fibers (× 350). *B*, kidney with marked degeneration of tubular epithelium (× 350). *C*, pancreas with extensive uniform necrosis of parenchyma (× 200).

did we find an extensively engorged and tense liver at necropsy examination.

Directly related to the acuteness and severity of the cardiac decompensation, the pancreatic lesion may be mild or extensive. If mild, recovery occurs with reëstablishment of circulatory compensation; we have mute evidence of this through the observation of fine to coarse, patchy fibrosis in the gland in cardiac cases with a history of repeated decompensation and with very little arteriosclerosis to account for scarring on that ground *per se*.

The pathogenesis of the pancreatic necrosis and hemorrhage in the congestive heart failure group appears to be clear-cut. Acute circulatory stasis in the organ leads to anoxemia in the tissue and increase in its hydrogen-ion concentration. This in turn disturbs the oxidized and reduced sulphydryl balance; in an attempt to supply oxygen to the already anoxemic tissue, oxidized sulphydryl becomes reduced, thereby augmenting the concentration of the latter, which acts as a catalytic agent for activation of trypsinogen in the acid medium (Waldschmidt-Leitz). In addition, in the autolysis of pancreatic cells, kinase is liberated, thereby furnishing a second activating calalyst (Morse). Lipase, being dependent both on an alkaline medium and on the presence of bile for its activation, is inert under the conditions existing here; hence, fat necrosis is not a feature of this group. A second factor, not so well established, however, is the increase in permeability of the upper intestinal mucosa due to its extreme congestion and degeneration, thus promoting the rate and decreasing the selectivity of absorption through this mucous surface; absorption of toxic products from the upper bowel may occur and enhance the acute degenerative changes seen in all of the viscera.

Pathologic Anatomy. Grossly the pancreas is always markedly congested, presenting a purplish-red color; the consistency is soft, either uniformly throughout or present in localized areas most frequent in the body. Punctate hemorrhages are often seen on the surface. The sectioned surface shows the areas of softness appearing as ill-defined, almost semifluid patches in which free hemorrhage is prominent. In those instances in which the degenerative process has occurred uniformly throughout, the organ is mushy and does not maintain its form; petechial hemorrhages are scattered diffusely.

Microscopic examination in the first instance shows focal areas of parenchymal necrosis lying in pancreatic tissue that is either normal or only moderately degenerated. In the latter type necrosis is almost uniform throughout; some areas, however, are degenerated to a less degree. Hemorrhage is not as evident microscopically as macroscopically, the blood cells sharing the fate of the parenchymal elements; this is more especially true in the severe instances. (The question of postmortem autolysis has arisen in this connection;

Summarizing Table of Collected Data.

			Inflammatory.		Degenerative.				
			Dependent on infection and/or obstruction of the biliary tract.	Dependent on infection from contiguous structures.	Dependent on cardiovascular disease.			Dependent on general toxic phenomena.	Dependent on trauma to the pancreas.
					Congestive heart failure type.	Hypertensive arteriosclerotic.	Embolic.		
	Number of cases in series		3	2	8	6	0	11	0
	Average age		55 years	47 years	57 years	56 years	—	42 years	—
	Sex		2 male. 1 female	2 male	2 male. 6 female	4 male. 2 female	—	6 male. 5 female	—
	Color		3 white	2 white	6 white. 2 black	4 white. 2 black	—	5 white. 6 black	—
Past symptomatology	Cardiac	Congestive	Negative	Not significant	Dyspnea, cough, ankle edema, arrhythmia, occasional headache and vertigo. Some history of acute decompensation	Occasional dyspnea and ankle edema		Negative	
		Hypertensive	Negative		Negative	Hypertension, headache, vertigo, precordial pain		Negative	
	Abdominal		Recurrent attacks of upper abdominal pain radiating to back; nausea, vomiting; "dyspepsia"		Epigastric pain with previous decompensation	Abdominal claudication and vomiting (occasional)		Negative	
	Cerebral		Negative		Negative	Old hemiplegia (1 case)		Epilepsy (2 cases) Paresis (1 case) Alcoholism (1 case)	
	Miscellaneous symptoms		Leukocytosis; chills, shock and *collapse*		Elevation of blood sugar level, terminal shock and *collapse*			Increased blood sugar level, *sudden death* (often unexplained)	
Present symptomatology	Cardiac	Congestive	Dyspnea and patchy cyanosis	Dependent on primary structure involved. No generalization can be made	Aggravation of old congestive phenomena with pleural effusion and ascites.	Dyspnea, cyanosis, cough, hemoptysis, slight edema		Negative	
		Hypertensive	Negative		Negative	Overshadowed by congestive features		Negative	
	Abdominal		Sudden onset of excruciating epigastric pain with nausea, vomiting and distention; tenderness in upper abdomen and costovertebral angle. (Right upper quadrant pain in 2 cases)		Epigastric pain radiating to back and loins. Nausea and vomiting	Acute epigastric pain, radiating to back, loins and occasionally to anterior lower left chest. Nausea and vomiting		Acute epigastric pain, radiating to back and/or chest; extreme nausea, vomiting and diarrhea	
	Cerebral		Terminal psychotic delirium (1 case)	Dependent on primary structure	Stupor	Occasional hemiplegia		Stupor. Loss of sphincteric control. (Concomitant with meningi-	

Recent	Cerebral	Terminal psychotic delirium (1 case)	Dependent on primary structure involved. No generalization can be made	Stupor	Occasional hemiplegia		Stupor. Loss of sphincteric control. (Concomitant with meningitis, tetanus or pneumonia—1 case each)	
Pathologic anatomy	Pancreas	Large, firm, friable, patchy red-black, with fat necrosis in pancreatic bed and mesentery. Hemorrhage at mesenteric base. Bloody, acrid peritoneal fluid	Suppurative peripancreatitis with focal softening	Normal size; focal or diffuse softening; cyanotic, with focal or diffuse hemorrhage. No fat necrosis. No peritoneal exudative reaction	Normal size; focal to massive diffuse hemorrhage (intra- or peripancreatic) with focal or diffuse necrotic softening. Gross arteriosclerosis notable. No peritoneal fluid, no fat necrosis		Normal size; uniformly soft and mushy; dark purplish-red, with scattered hemorrhages; slight perilymphnodal fat necrosis in mesentery; no peritoneal fluid	
	Liver	Large (av. wt. 2500 gm.); soft and yellow	Negative	Congestion. Mild degeneration	Congestion. Occasional cirrhosis		No characteristic changes	
	Gall bladder and ducts	Chronic cholecystitis; many small, shot-like calculi (2 cases). Ducts patent (3 cases)	Negative	Usually negative. Occasional large calculus	Negative		Negative	
	Heart	Av. wt. 373 gm.; no constant lesion; av. blood pressure—100/70 (1 case), not obtainable (2 cases)	Negative	Av. wt. 525 gm.; soft, flabby, dilated; occasional chronic valvular lesion; occasional coronary disease (non-occlusive); av. blood pressure 147/78	Av. wt. 542 gm.; firm, concentric hypertrophy; coronary sclerosis; no occlusion; av. blood pressure 237/110		Av. wt. 340 gm.; extremely soft and flabby; no other notable lesions; av. blood pressure 129/63	
	Arterial tree	Negative	Negative	Slight to moderate sclerosis	Marked generalized sclerosis; mesarteritis degenerativa (1 case)		Negative	
	Other viscera	Show the extreme capillary congestion of "shock," esp. lung and kidney	Depend on primary lesion	Congestive phenomena; mild degenerative changes	Congestion and hemorrhage; arteriosclerosis		Marked toxic nephrosis	
Histopathology	Pancreas	Purulent exudate in and/or about ducts (visible where necrosis is incomplete); extreme irregular necrosis of parenchyma and fat; interstitial hemorrhage; (pancreas usually the seat of fatty infiltration)	Suppurative peri- or interlobular pancreatitis with little involvement of parenchyma early	Focal or diffuse necrosis; congestion and scattered hemorrhage; scarring in recurrent cases; no fat necrosis; no inflammation	Hemorrhage, necrosis and extreme arterio-arteriolosclerosis (occasional occlusion and visible rupture); no fat necrosis; no inflammation		Fairly uniform necrosis with scattered, partly digested hemorrhage; occasional slight fat necrosis; no inflammation	
	Liver	Subacute to subchronic periportal hepatitis, marked fatty metamorphosis	Negative	Acute and chronic passive congestion; no periportal hepatitis	Acute passive congestion; proliferative periportal hepatitis with cirrhosis (3 cases)		Parenchymatous degeneration; acute passive congestion	
	Other viscera	Extreme congestion	Depend on primary lesion	Marked myocardial degeneration	Coronary sclerosis, myocardial degeneration		Marked myocardial degeneration; necrotic nephrosis	

Chiari felt that necrosis seen in our degenerative classes was agonal or postmortem "Autodigestionsnekrose;" to this Gruber agrees. In our laboratory the bodies are handled uniformly and refrigerated promptly after death; we have examined the pancreas 3 to 6 days postmortem and have found that organ well preserved. Gruber notes in this type of case a diffusion of iron throughout the tissue, demonstrable by the Turnbull blue reaction, yet classes the necrosis agonal or postmortem; we feel that this observation would suggest strongly the congestive origin of the necrosis). The other viscera, especially the heart and kidneys, to a lesser extent the liver, show a rather marked degree of acute degeneration, rather more than would be expected as a result of the congestive phenomena alone. The gall bladder and bile ducts (both intrahepatic and extrahepatic) show little or no evidence of infection. Occasionally calculi may be found in the gall bladder, but they are usually of larger size, not capable of traversing the duct.

2. *Hypertensive Arteriosclerotic Type.* The occurrence of sudden, severe, epigastric pain in a hypertensive individual should suggest so-called pancreatic apoplexy, sometimes associated with cerebral apoplexy and occasionally with the dissecting aneurysm of "mesarteritis degenerativa sine syphilis" (one of our cases showed this latter condition, with dissection along the branches of the cœliac axis). Phenomena of cardiac decompensation are not prominent in this type of case, but usually appear if the lesion is severe and the case terminates fatally. These cases, as well, may present minor lesions that heal with residual scarring of the organ, but are differentiated histologically from the congestive type by the prominence of vascular sclerosis or arteritis in the pancreas and other organs.

The hemorrhage and concomitant local necrosis in the pancreas are the result of a ruptured vessel; this may be due simply to the combination of hypertension and diseased vessels poorly supported in the loose parenchyma of the organ, or it may be initiated by the excessive vomiting of the gastrointestinal crises or of the uremia so characteristic of arterionephrosclerosis with renal failure.

Pathologic Anatomy. The pancreas is usually not enlarged; the apoplectic lesion is often not visible until the cut surface is examined, although the local area of softening may be palpable. Sometimes, however, the head lies in a massive peripancreatic hemorrhage. The lesion is more often single and situated in the head; less often is the hemorrhage massive within the organ, spreading along the interstices with extreme destruction of the parenchyma. Histologically, vascular sclerosis, senile or arteritic, is the striking feature; occasionally one is fortunate enough to observe actual breaks in the arteries and veins. Hemorrhage occupies the foreground of the picture and necrosis is less prominent than in the preceding group (thus, hemorrhage alone is not the prime factor in the cause of necrosis, as other conditions mentioned above are

necessary therefore). Necrosis under these circumstances is primarily a pressure necrosis; secondarily, anutritional; finally, to a lesser extent, enzymal.

The other viscera in these apoplectic cases do not show degenerative changes unless from some extraneous factor. Vascular disease of other organs, however, is usually striking. Here again, disease of the biliary tract is not a feature.

In none of our cases was pancreatic apoplexy associated with coronary occlusion, although the clinical features in some instances suggested that that phenomenon has occurred; some reached the necropsy table with the diagnosis of coronary occlusion, some with the diagnosis of mesenteric thrombosis. These latter two vascular accidents tax the diagnostic acumen.

3. *Embolic Type.* We have had no experience with this group. It is almost invariably associated with subacute bacterial endocarditis, the pancreas sharing to a lesser extent the embolic accidents of other viscera. (Hematogenous pancreatitis should receive mention, although it is rather rare; it is a question whether to class it with this group or with the inflammatory group, depending on whether one considers it due to minute bacterial emboli.) For a complete study of infarctive phenomena in the pancreas in heart disease reference is made to the article of Gerlei.

(*b*) Dependent on General Toxic Phenomena. This group is identified positively only at necropsy examination by the presence of an extremely necrotic pancreas in association with an almost equally marked necrosis of the other viscera, in the absence of cardiac or vascular lesions, due to an ingested or unknown toxin. Most of the cases in our series were associated with some intracranial disease (acute alcoholic psychosis, pneumococcus meningitis, epilepsy, paresis, thrombosis, etc.) that we believe, for the most part, is either concomitant (and dependent on the same etiologic agent) or merely coincidental.

Persistent nausea and vomiting appeared to be the most common subjective symptom of this group, sometimes associated with intense upper abdominal pain (the latter was not elicited in some instances on account of stupor). In many cases gastrointestinal symptoms were attributed by the clinician to the associated intracranial phenomena, some to intestinal obstruction or ruptured viscus. Almost uniformly, blood sugar was markedly increased. Uniformly the patients went into collapse and died.

Pathologic Anatomy. The pancreas is extremely soft and necrotic throughout; hemorrhage is not prominent, although the organ is a dusky red color. Histologically the architecture is lost, only shadows of acini are visible; not the slightest evidence of acute inflammation is seen. Very slight fat necrosis may be present in the periphery of the gland. (Two cases showed fat necrosis surrounding lymph nodes in the mesentery; this was attributed to

retrograde lymph flow from the pancreas carrying lipase with it.) Other viscera suffer in proportion; the heart invariably shows an extremely extensive acute myocardial degeneration; invariably the kidneys are the seat of necrotic nephrosis. The liver cords are converted into an almost anuclear, homogeneous mass; some cases show a lesser degree of damage where death occurs rapidly. The gastrointestinal tract suffers markedly in this type of case; the stomach is dilated and filled with regurgitated bile and the mucosa of the stomach and intestines is exceedingly congested and often necrotic, sometimes showing histologically an inflammatory reaction in the submucosa.

(*c*) DEPENDENT ON TRAUMA TO THE PANCREAS. Opie has stated: "Hemorrhagic and gangrenous pancreatitis with disseminated fat necrosis has in a few instances so directly followed abdominal injury that the relation to traumatism cannot be doubted. Injury to the pancreas is usually associated with such severe damage to adjacent structures that a fatal result is rarely referable to the gland. Incisions into the pancreas of animals heal readily." It has been shown experimentally that obstruction to the circulation associated with injury to the parenchyma may be followed by hemorrhagic necrosis of the pancreas; this suggests that traumatic thrombosis of blood-vessels may play a part in the pathogenesis.

Comment. Rational treatment of acute hemorrhagic necrosis of the pancreas depends entirely upon a clear conception of its etiology and of the various forms in which it may exist. In the inflammatory type prompt, intelligent surgical intervention is imperative; in all other instances surgery seems to be definitely contraindicated. Those cases associated with congestive heart failure require heroic therapy directed toward restoring circulatory compensation; the hypertensive group calls for measures directed toward the underlying cause. For the toxic cases little can be done unless the noxious agent can be identified and eliminated.

During a discussion of so-called "acute hemorrhagic pancreatitis" recently, a surgeon mentioned the fact that he had of late become more conservative in advising operation in certain cases, having observed recovery in instances without surgical intervention. We believe that these latter were cases that fall in our degenerative group and that the surgeon had unconsciously come to recognize it without knowledge of the underlying features. How many surgeons, examining a patient with severe upper abdominal pain, nausea, vomiting and sometimes collapse, would advise against exploratory laparotomy? Fortunately modern surgery is moving slowly toward a policy of conservatism.

If the patient is viewed through a wide-angle lens rather than through one of short focal length (and that focus centered between the umbilicus and xyphoid) fewer patients will be subjected to and their death hastened by unnecessary operation.

Summary. A simple classification of acute hemorrhagic necrosis of the pancreas has been evolved in which etiology, pathologic anatomy and clinical manifestations are closely bound, as follows:

I. INFLAMMATORY.
  (*a*) Dependent on infection and/or obstruction of the biliary tract
  (*b*) Dependent on infection of contiguous structures.

II. DEGENERATIVE.
  (*a*) Dependent on cardiovascular disease.
    1. Congestive heart failure type.
    2. Hypertensive arteriosclerotic type.
    3. Embolic type.
  (*b*) Dependent on general toxic phenomena.
  (*c*) Dependent on trauma to the pancreas.

The relation of this classification to treatment has been discussed.

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THE ABSENCE OF OSTEOPOROSIS DEMONSTRATED CHEMICALLY IN CLINICAL HYPERTHYROIDISM.*

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THE work of Aub and his coworkers, in 1926, in investigating the influence of the thyroid gland on the metabolism of calcium showed that patients whose diets were deficient in calcium but were adequate in other respects had a negative calcium balance. Patients

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TABLE 1.—PARTIAL SUMMARY OF DATA EXPRESSED IN AVERAGES.

Age, group.	Number of controls, with sex.	Specimen.	Percentage of ash in dry bone.				Percentage of calcium in ash.				Percentage of phosphorus in ash.				Calcium to phosphorus ratio.			
			Control.		Patient with hyperthyroidism.		Control.		Patient with hyperthyroidism.		Control.		Patient with hyperthyroidism.		Control.		Patient with hyperthyroidism.	
			Male.	Female.	Male.	Female.	Male.	Female.	Male.	Female.	Male.	Female.	Male.	Female.	Male.	Female.	Male.	Female.
15–20	3 F	Rib		57.4		56.8		37.73		37.55		17.36				2.17		
		Pelvis		55.3		51.9		38.26		36.90		18.19		17.31		2.11		2.13
22–23	2 F	Rib		58.0		56.2		38.46		37.60		18.30		17.81		2.10		2.11
		Pelvis		54.5		54.1		39.06		37.30		17.87		16.90		2.19		2.20
30–33	4 F	Rib		58.9		56.1		37.52		40.17		17.57		19.28		2.14		2.08
		Pelvis		54.9		48.6		37.59		39.40		17.48		17.12		2.15		2.30
34–37	3 F	Rib		60.1		50.4		38.81		37.40		17.60		16.51		2.13		2.26
		Pelvis		54.8		52.2		37.28		36.82		17.92		18.35		2.09		2.00
37–38	2 F	Rib		55.9		54.6		37.53		39.80		17.15		18.18		2.16		2.19
		Pelvis		52.1		48.4		39.17		38.40		18.20		18.29		2.15		2.10
37–42	5 F	Rib		58.0		57.8		37.30		34.83		17.74		18.38		2.09		1.90
		Pelvis		53.2		50.5		37.81		36.78		17.81		18.33		2.13		2.00
40–46	3 F 5 M	Rib	53.5	54.3		49.4	38.43	38.97		37.70	18.43	18.11		18.90	2.06	2.11		1.99
		Pelvis	52.4	52.3		55.5	37.38	37.08		37.10	18.06	17.63		18.70	2.03	2.07		1.99
46–50	4 F 5 M	Rib	51.3	56.4	57.8	61.8	36.59	39.05	36.80	36.85	17.23	17.75	14.71	17.78	2.19	2.19	2.50	2.07
		Pelvis	51.1	55.1	57.3	57.8	37.87	37.52	37.37	37.38	17.41	17.55	17.32	17.78	2.16	2.14	2.12	2.10
50–56	4 F 5 M	Rib	54.5	55.6	50.6	54.2	40.38	36.31	38.70	37.40	19.20	17.78	18.39	18.18	2.12	2.03	2.10	2.07
		Pelvis	56.5	54.3	51.4	54.6	37.55	38.77	37.32	39.42	17.66	18.10	18.67	17.47	2.13	2.14	2.00	2.26
55–58	5 F 4 M	Rib	49.5	46.9	47.8	52.2	38.63	40.56	37.25	35.10	17.14	18.04	17.20	16.87	2.25	1.96	2.16	2.08
		Pelvis	49.3	51.6	51.4	49.4	37.82	37.53	37.60	36.35	17.93	17.51	16.89	17.80	2.11	2.14	2.22	2.04
60–62	2 F 6 M	Rib	45.9	41.7	45.2	44.4	37.77	40.11	37.90	38.60	17.70	18.06	17.10	18.75	2.19	2.15	2.22	2.06
		Pelvis	46.2	42.8	37.3	42.4	38.08	37.30	41.20	37.20	17.75	17.74	19.21	18.69	2.12	2.08	2.12	1.99
63–65	2 F 2 M	Rib	42.4	50.4	40.7	35.2	38.80	37.29	38.21	36.10	17.79	17.80	18.42	18.45	2.19	2.09	2.07	1.96
		Pelvis	35.3	53.9		36.0	38.33	36.20		39.74	17.85	18.27		17.85	2.13	2.05		2.22
66–68	3 M	Rib	53.9			46.6	37.35			33.17	17.71			17.02	2.11			1.95
		Pelvis	49.2		40.2	51.4	37.01		38.80	37.80	17.27		17.78	17.06	2.14		2.18	2.21
70–75	2 F 6 M	Rib	42.2	44.3	41.9		37.35	37.61	37.69		17.78	18.50	17.86		2.10	2.15	2.11	
		Pelvis	45.6	44.8	40.2		37.25	37.85	37.36		17.92	17.94	17.90		2.07	2.08	2.08	
Final averages		Rib	49.1	53.6	47.3	51.9	38.16	38.17	37.76	37.09	17.87	17.82	17.28	18.01	2.15	2.11	2.19	2.06
		Pelvis	48.2	52.3	46.3	50.2	37.66	37.80	38.27	37.73	17.73	17.86	17.96	17.82	2.11	2.12	2.12	2.12

with either exophthalmic goiter or adenomatous goiter with hyperthyroidism, as well as normal persons whose metabolism had been elevated by administration of thyroxin or thyroid extract, excreted considerably more calcium than the control subjects. In the instance of one patient with exophthalmic goiter, whose basal metabolic rate was high, the output of calcium was increased approximately fivefold. Excretion of phosphorus behaved similarly, but to a lesser degree. These experiments tended to indicate that the excreted calcium was of endogenous origin, and that its probable source was the bones. This possibility was offered by Aub and his coworkers in their roentgenologic studies, and has been demonstrated, also, by Plummer and Dunlap and by Dunlap and Moore, who have observed decreased density of the bones of patients with exophthalmic goiter. Osteoporosis was found to affect the entire osseous system, especially the spongy bones and those with superficial coverings, such as the skull, ribs and bones of the extremities. In the extremities it was more noticeable in the epiphysis and ends of the diaphysis than elsewhere. The loss of calcium varied in degree from that producing only a slight increase in translucence, so trivial as to escape casual notice, to marked and unquestionable rarefaction. Slight changes became apparent by photographing the hand of the patient on the same plate, or by the same technique, as that of a normal person. When absorption of calcium was more pronounced, the shadow cast by the bone was faint, the trabeculæ were not very distinct and the bone appeared structureless. The change was more diffuse than localized, and if it was localized it called for differential diagnosis from atrophy, malignancy, infection, etc. The view was expressed that the degree of decalcification was in direct relation to the severity and duration of the hyperthyroidism, and that decalcification was usual rather than unusual. Aub, Bauer, Heath and Ropes elaborated the previous work, but reached the same conclusions with reference to the effect of hyperthyroidism, on structure of bone, and elimination of calcium. In some instances loss of calcium was greatly in excess of the increase in basal metabolic rate.

The possible criticism which might be offered in drawing definite conclusions from the roentgenologic studies would be in the selection of the controls, since it is well known that the degree of activity, occupation and other factors, as well as age and sex, influence density of bone.

It has been found that administration of iodin, and partial removal of the thyroid gland or of the toxic adenoma, tend to cause return of the calcium balance toward normal. Aub, Bauer, Heath and Ropes stated: "It is not to be expected that all cases of hyperthyroidism would show osteoporosis of the bones because of this increased calcium elimination, which could probably be compensated for by a diet containing an adequate amount of

calcium. In some cases of long duration, however, this increased calcium loss from the bones may be apparent in Roentgen ray pictures." They concluded that the change in the bones was attributable to withdrawal of calcium phosphate, although they admitted the possibility that some of the calcium might be in the form of calcium carbonate. The ratio of calcium to phosphate indicated that tricalcium phosphate was the form in which most of the mineral matter was lost. The elevation of the basal metabolic rate was not in itself the cause of the loss of mineral.

With this work as a background, it occurred to the authors that if such gross differences were present in the bones of persons with hyperthyroidism as to be demonstrable by roentgenogram, it might be possible to demonstrate directly that the increased amount of calcium and phosphorus excreted could be shown to be derived from bones by analysis of bones removed from patients who had died and who had presented a history of hyperthyroidism. Also, data thus secured would demonstrate whether the decrease in density was due to loss of calcium and phosphorus as tricalcium phosphate, with a resultant high percentage of calcium carbonate remaining, or whether decreased density exists because of porosity due to the presence of an increased amount of organic matter. Naturally, many factors were involved in the selection of such cases, and it was apparent at the outset that much negative evidence might be accumulated. Factors such as duration of the disease, whether operation had been submitted to, the length of time since operation, the basal metabolic rate, etc., offered complications in drawing conclusions from the analytic data obtained by analysis of the bones. However, it was deemed advisable to proceed to obtain these data, with the hope that the results could be correlated with the clinical history, and that positive evidence could be obtained by association between the osteoporosis of hyperthyroidism as observed clinically and the disease as a whole.

Methods. Two samples were removed in each case, one from the right fifth rib, adjacent to the place where it would be severed at necropsy (performed as a routine) and the other from the left superior ramus of the pubic bone. The former was believed to reflect bony changes most readily, whereas the latter was assumed to be the least affected of any portion of the available bony system. The data which it was deemed advisable to secure included specific gravity, content of moisture, total solids, mineral matter, organic matter, content of calcium, content of phosphorus and the calcium to phosphorus ratio. Determinations of magnesium also were made, but the results seemed to be of no significance.

Because of the infrequency with which patients who present recent histories of hyperthyroidism come to postmortem examination, collection of material extended over 3 years, necessitating that the samples of bone be placed in 95 per cent alcohol for temporary

storage. This solution was found to be superior to formaldehyd because the periosteum could be more readily removed in cleaning the final samples for examination. This mode of preservation tended to remove some of the water content of the bone, but the defect was partially remedied by leaving the bone in water for a day before weighing or measuring its volume. This procedure probably did not accurately restore the bone to its original condition, but the advantages outweighed the disadvantages, and the results of the various determinations are at least comparable.

However, in evaluating the final data it seemed advisable to consider only those data based on the dry bone material, for the content of moisture and determinations of specific gravity, although interesting in themselves, offer no solution to the problem. Determinations of moisture were made by drying at 110° C. Specific gravity was determined from the weight and the volume as measured by displacement of a column of water in a graduated buret.

The samples taken from the ribs were uniform in character; care was taken to eliminate as far as possible variations in weight, such as would occur if the ends of the fragments were not uniformly cut across. One would, therefore, expect comparable and reliable results from this source. The ramus of the pubis, on the other hand, was subject to considerable variation in the size and shape of the fragment secured. Effort was made to preserve the most dense portion of the bone, but variation occurred in spite of every precaution. In evaluation of the results account must be taken of this variability.

The dry weight of the sample was determined by differential weighing in crucibles, following which it was incinerated in an electric furnace. The loss of weight represented organic matter; the residual weight was ash.

To determine the mineral content, the ash was dissolved in hydrochloric acid, made up to a volume of 100 cc., and the resulting solution was set aside for chemical examination. Aliquot parts of this solution were taken for determination of calcium and phosphorus. Determinations of calcium were made on portions of 3 cc., according to the procedure of Kramer and Howland, and determinations of phosphorus were made on portions of 1 cc., according to the procedure of Bell and Doisy.

Table 1 is a condensation of the more essential analytic data obtained. The values for specific gravity and content of moisture have been omitted, because correlation between the results of analysis of control specimens and of specimens from patients with hyperthyroidism seemed impossible. Study of the statistical data warranted its presentation by averages. Consequently, in the various age groups the average values are given. No constant difference is apparent in either the percentage of ash, percentage of calcium or phosphorus or the calcium to phosphorus ratio. However, as

seen from the general average, there is a tendency to higher mineral content in the control cases than in the cases of hyperthyroidism. This increase in ash is not of sufficient magnitude to be obvious in roentgenograms. The calcium to phosphorus ratio is slightly greater than 2. In some cases of hyperthyroidism the calcium to phosphorus ratio is greater than that of the controls, but this is not constant, and no particular significance can be attached to it. That the value is not 1.93, as in dry bone or apatite, is due to the fact that the results were obtained on incinerated material from which carbon dioxid was lost. If constant, marked osteoporosis existed, one would expect a calcium to phosphorus ratio considerably greater than 2. This was obtained in 1 control case, in which the calcium to phosphorus ratio was 2.62. The subject presented clinical osteoporosis, but no hyperthyroidism. One other instance of a high calcium to phosphorus ratio was found in a case of hyperthyroidism. The bone from the rib, in this case, had a calcium to phosphorus ratio of 2.5, whereas the ratio in the pubic bone was normal.

TABLE 2.—SUMMARY OF DATA CONCERNING PATIENTS WITH HYPERTHYROIDISM FROM WHOM SPECIMENS OF BONE WERE SECURED.

Case No.	Age, years, and sex.	Type of hyperthyroidism.	Duration of disease.	Type of thyroidectomy and weight of removed tissue in grams.	Time of death after operation.	Basal metabolic rate.
1	18 F	Exoph. goiter	8 months	Subtotal; 267	2 days	+108
2	22 F	Exoph. goiter	3 years	No operation	No oper.	+80
3	32 F	Rec. exoph. goiter	3.5 years	Subtotal; 8	6 months	+57
4	34 F	Goiter*	Unknown	Unknown	1 year	
5	36 F	Exoph. goiter	6 months	Partial; 20	1.5 months	+40
6	40 F	Exoph. goiter	3 months†	Subtotal; 86	4 days	+31
7	46 F	Exoph. goiter	9 months	Subtotal; 50	16 days	+83
8	48 M	Exoph. goiter	2 months	Subtotal; 12	9 days	+45
9	48 F	Exoph. goiter	4 months	Resection of rt. lobe; 62	15 hours	+57 +64
10	53 M	Exoph. goiter	18 months	No operation	No oper.	+41
11	53 M	Exoph. goiter	4 months	Subtotal; 54	2 days	+47
12	53 F	Exoph. goiter	3 months	No operation	No oper.	+49
13	57 F	Exoph. goiter	1 year	Subtotal; 100	2 days	+60
14	58 M	Toxic adenoma	7 years	Unknown; operation elsewhere	5 years	
15	58 F	Toxic adenoma	1 year	Subtotal; 70	2.5 years	+10
16	60 M	Toxic adenoma	4 months	Subtotal; 35	19 months	+51
17	63 F	Toxic adenoma	3 months	No operation	No oper.	
18	65 F	Hypertr. adenoma	2 years	Subtotal; 47	3 days	+71
19	66 M	Exoph. goiter	8 months	Subtotal; 56	3 days	+64
20	68 F	Adenoma	4 months	Subtotal; 32	4 years	+17
21	70 M	Hyperthy.	2 years	Subtotal; 126	8 days	+38
22	71 M	Toxic adenoma	Unknown	No operation	No oper.	+20
23	72 M	Exoph. goiter	2 years	Subtotal	2 days	+29

* Type unknown, removed elsewhere 1 year before.
† Goiter present 22 years.

Table 2 is presented to show variable factors that may exist in cases of hyperthyroidism, which may lead to variable factors in structure of bone. For example, the time of death after operation varied from 15 hours to 5 years; the duration of the disease, as

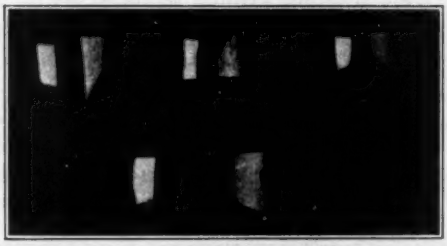

FIG. 1.—The specimens are of pubic bone (more dense) and of rib (less dense). The pair of specimens, below, was obtained from the patient represented in Case 1 (Table 2). The three pairs of control specimens, above, also are of pubic bone and of rib, and were obtained from subjects of the same sex and age group, but who did not have hyperthyroidism.

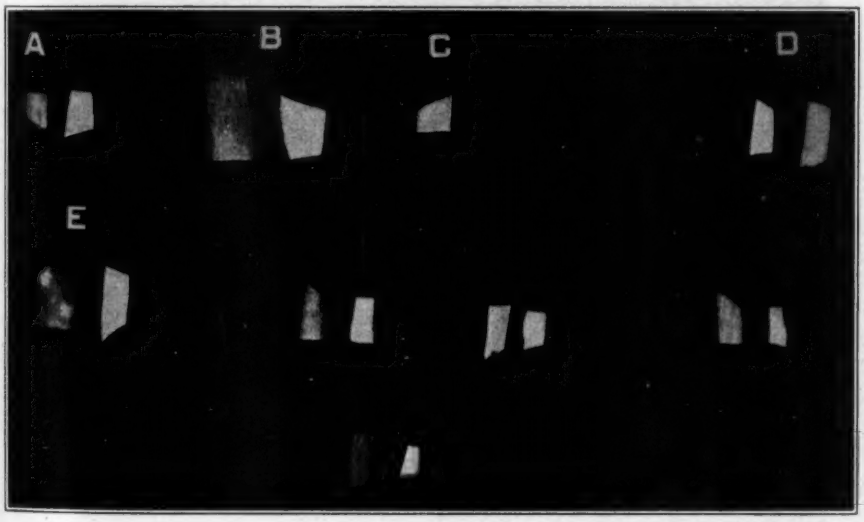

FIG. 2.—The specimens are similar to those in Fig. 1. The pair of specimens, below, was obtained from the patient represented in Case 7 (Table 2); the other specimens are controls, obtained from subjects of the same age group, but who did not have hyperthyroidism. Control specimens *A*, *B*, *C*, *D* and *E* were obtained from males, the unlettered control specimens from females. Specimen *C* is of rib.

elicited from the history, varied from 2 months to 7 years, and the basal metabolic rate from +10 to +108. Obviously, some of these persons would be more likely to present clinical osteoporosis than others, and one would expect that those patients who presented histories of moderately increased metabolism for a period of several

months, and whose death followed very soon after partial thyroidectomy, precluding any possibility of regeneration of bone, would show by roentgenologic examination decreased opacity of the bone. Roentgenograms of specimens in 4 such cases (Nos. 1, 17, 18 and 19, Table 2) are shown in Figs. 1, 2 and 3. They represent in Table 1, respectively, the age groups 15 to 20 years, 40 to 46 years, 63 to 65 years and 66 to 68 years. These pictures demonstrate no apparent difference in opacity between the specimens from patients with hyperthyroidism and the controls. Table 1 also does not disclose striking variations in content of ash or in calcium to phosphorus ratio. Case 4, however, is a case of osteoporosis in which the calcium to phosphorus ratio was found to be 2.62.

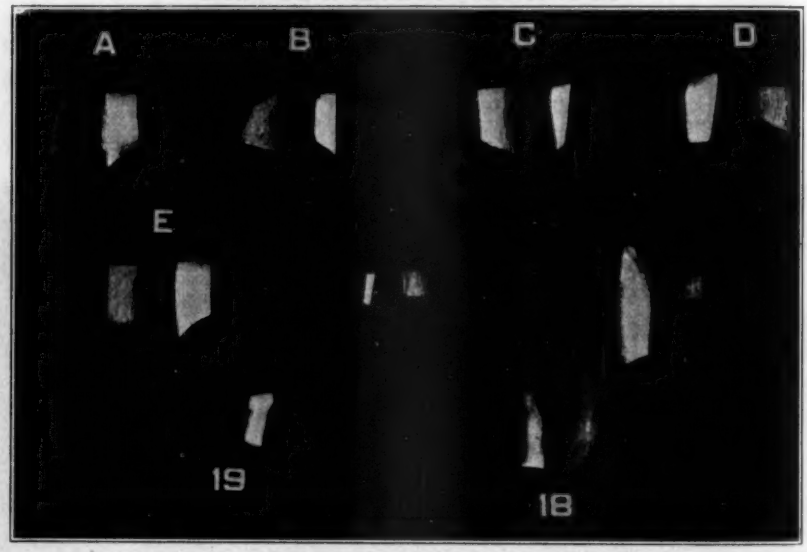

FIG. 3.—The specimens numbered 18 and 19 were obtained, respectively, from the patients represented in Cases 18 and 19 (Table 2). The general plan is the same as that of Figs. 1 and 2. Control specimens, obtained from subjects of the same age group, but who did not have hyperthyroidism are represented. Specimens *A*, *B*, *C*, *D* and *E* were obtained from males and are to be compared with specimen 19. The unlettered control specimens were obtained from females and are to be compared with specimen 18.

Summary. It has been shown previously that hyperthyroidism may produce excretion of endogenous calcium, which may result in osteoporosis demonstrable by roentgenogram.

In this study, chemical and roentgenographic study of bone, removed postmortem from 23 patients who had had histories of hyperthyroidism, and from 78 control subjects, failed to demonstrate a sufficiently constant difference in percentage of ash, percentage of calcium, calcium to phosphorus ratio or roentgenographic opacity

to warrant a conclusion that hyperthyroidism is always accompanied by some degree of osteoporosis.

Failure to demonstrate a difference may be explained by assuming that there was compensatory ingestion of calcium, or other variable factors that may occur in clinical hyperthyroidism. Obviously, ingestion of calcium is not controlled in clinical hyperthyroidism as it may be controlled in experimental hyperthyroidism. Further work of this nature in clinical hyperthyroidism seems unnecessary, since the results apparently can be only inconclusive.

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TWO METHODS OF INVESTIGATING DISEASES OF THE CORPUS STRIATUM.

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The so-called extrapyramidal system, the corpus striatum in the widest sense, occupies an important position in neurologic medicine. Not only do the physiology and pathology of this part of the brain hold many unsolved problems in general as well as clinically, but at the same time these problems touch to an unusual degree upon those domains of medical science which are outside neurology.

One difficulty which often arises in clinical work is to decide whether or not a certain disease picture contains a "striatal" factor or not. This is especially the case when it may be supposed to have epidemic encephalitis as an etiologic basis, and when there are no indisputable symptoms in favor of an extrapyramidal lesion.

This difficulty might be solved if it were possible to work out a method which demonstrates diseases of the striatum with certainty, even when they cannot be found clinically.

The authors have earlier, and independently of each other, indicated two different methods of investigation which are thought to attain this object.

I. A.L.S.R. (*Adrenalin-Liquor-Saccharum Reaction*) (Munch-Petersen's Method). This test is based upon the fact that a hyperglycemia caused by adrenalin, or by adrenalin administered with glucose, is followed by a rise in the sugar content of the spinal fluid as recovered on lumbar puncture.* This rise depends somewhat on the size of the rise in the blood sugar, but if the latter reaches about 0.16 per cent or more a maximal rise in the sugar of the lumbar puncture fluid is obtained under the experimental conditions given. The normal limits of the rise may be reckoned: upper limit, 0.03 per cent; lower limit, 0.015 per cent. The experiment must be carried out on an absolutely fasting patient, and the puncture for the determination of the rise in the sugar of the spinal fluid must be carried out after 2½ hours.

The test is performed as follows: In the morning (after a 12-hour fast) determinations of the blood sugar and spinal fluid sugar are made. The patient then takes 50 gm. of glucose in water (about 150 cc.), and 5 to 10 minutes later is given a subcutaneous injection of 0.5 mg. adrenalin. A determination of the blood sugar is then made every hour, in order to make sure that the rise is high enough. Two and a half hours after the adrenalin injection the blood sugar and spinal fluid sugar are again estimated. As mentioned, the spinal fluid sugar will normally at this time of the experiment have been increased by 0.015 to 0.03 per cent. One may, for instance, find a fasting value of the spinal fluid sugar of 0.05 per cent to have risen to 0.07 per cent. Under pathologic conditions it is found that this increase may be smaller or greater.

Munch-Petersen,[1] on the basis of a large number of observations, interprets a smaller rise as a definite sign of a direct "striatal" affection. A greater rise may also be due to this, but may also be caused by affections outside of the striatum. It may be, however, that the greater rise is caused by an indirect influence upon the functions of the striatum.

II. B.F.I. (*Bimanual Faradic Irritation*) (Wernøe's[2] Method). This test is based upon the well-known motor influence which is caused when a faradic current is lead simultaneously through the palms of both hands. On account of the contraction of the muscles of the upper extremity we get: (1) pronation, (2) flexion of the wrist joint and (3) flexion of the elbow.

On the basis of numerous experiments, Wernøe believes that the

* A pure glucose-hyperglycemia does not cause any rise, or at any rate, a much smaller rise than the hyperglycemia after adrenalin.

reflex is indicated from the sensory tracts of the lower arm. Furthermore Wernøe is of opinion that the highest point of the reflex must be situated in the striatum: (1) because affections of the cortex do not influence the normal course of the reflex; (2) because the reflex disappears with crossed spinal sensory paralysis; (3) because patients with affections of the corpus striatum, but without symptoms arising in other parts of the central nervous system, generally show atypical or absent movements of the arm on bimanual faradic irritation.

Wernøe has previously shown that faradic irritation also causes a cortically induced inhibitory reflex of the motor functions. This explains various atypical responses in patients with either functional pareses or anesthesias.

Wernøe distinguishes between cortically and striatally induced functional atypical responses. The former cause normal, but increased, reactions, often combined with rhythmical movements of the arms, as the result of cessation of the inhibition or of a discontinuous inhibition from the cortex. The latter cause either decreased, absent or altered, grotesque, writhing and unbalanced movements, very likely because of anomalies in the conduction of the striatum.

In cases of organic, striatal affection, the reflex may, as we have mentioned, be absent, or atypical movements may appear, such as extension of the wrist, supination, extension of the elbow and the like.

Neither of the two methods described here have as yet been so thoroughly tested that they can be called pathognomonically certain in their results. We must especially emphasize that a "normal" reaction does not exclude an affection of the striatum. It would, however, be of great importance in evaluating the methods to examine their reciprocal agreement.

It cannot be expected *a priori* that two methods, so different, should agree entirely in their results. Their mechanisms are too far apart for this. On the other hand, it must be said that agreement in a sufficient number of cases, the nature of the cases being duly considered, will give strong reciprocal support to the postulated use of the two methods, which furthermore in certain cases may be used to supplement each other. In reality we here have two experimental methods, which in all respects are independent of each other, one of them being biologic-chemical, the other more clinical, the aim of both, however, being the same: to prove affections in the corpus striatum.

In the table below 33 cases, examined with both methods, have been collected. In 22 of these cases the two methods agreed well (67 per cent). In 7 cases the result of the two methods did not agree (21 per cent). In 4 cases the agreement cannot be judged (12 per cent).

TABLE 1.—ANALYSIS OF DATA OBTAINED BY THE TWO METHODS.

Number.	Diagnosis.	Spinal fluid.		Quotient, per cent.	A.L.S.R. reaction.	A.L.S.R. increased.	A.L.S.R. decreased.	A.L.S.R. normal.	B.F.I. reaction.		Remarks.	Correlation of tests.	
		C.	Glob. Alb.						Atypical.	Normal.		Agreement	Disagreement
1.	Encephalitis (chronic)	2/3	0–1–11	64	0.007		+		+		No reflex in spite of maximal irritation	+	
2.	Encephalomyelitis (chronic)	20/3	2 – 40	68	0.004		+		+			+	
3.	Encephalomyelitis (chronic)	15/3	0–1–10	68	0.012		+		+			+	
4.	Encephalomyelitis (chronic?)	14/3	2–3–17	71	0.032	+			+		Difference in reflexes, right hand reacts more intensely than the left	+	
5.	Encephalomyelitis (chronic)	3/3	1 – 13	54	0.010		+		+			+	
6.	Encephalitis	4/3	1 – 23	73	0.007		+		+			+	
7.	Spondylitis cervicalis tuberculosis	3/3	0 – 11	65	0.006		+		+			+	
8.	Encephalitis sequelæ	0/3	0 – 7	65	0.034	+			+		Extension of elbow + rhythmical tremor	+	
9.	Amyotrophic lateral-sclerosis	0/3	0 – 9	45	0.043	+			+		Flexion of elbow	+	
10.	Encephalitis	5/3	1–2–13	66	0.008		+		+			+	
11.	Encephalitis	1/3	0–1?–19	49	0.045	+			+			+	
12.	Encephalitis epidemica?	0/3	0 – 11	55	0.032	+			+			+	
13.	Encephalitis; tremor manuum	0/3	1?– 16	70	0.011		+		+		Tremor is inhibited	+	
14.	Encephalitis (chronic?); paralysis agitans?	1/3	0 – 9	77	0.004		+		+			+	

15.	Encephalitis	32/3	3 – 33	58	0.043	+			+			+	
16.	Tumor cerebri; glycosuria renalis	5/3	2 – 40	63	0.009		+		+		Difference in reflexes, right hand reacts more lively than the left	+	
17.	Paralysis agitans	2/3	0 – 9	58	0.029			+		+		+	
18.	Paralysis agitans	5/3	0 – 13	71	0.027			+		+		+	
19.	Paralysis agitans	1/3	0 – 12	68	0.026			+		+		+	
20.	Encephalitis epidemica (chronic)	2/3	0 – 12	92	0.011		+		+			+	
21.	Encephalitis?	10/3	1 – 16	76	0.014		+		+			+	
22.	Sclerosis dissemin.; glycosuria	30/3	2 – 18	77	0.014		+		+			+	
23.	Encephalitis (chronic); tremor manuum	1/3	1 – 12	69	0.011		+		?	?	Tremor increases	?	
24.	Encephalitis (chronic)	4/3	1 – 11	79	0.008		+		?	?	Rhythmic flexion of both elbow joints	?	
25.	Hysteria	0/3	1 – 17	66	0.013		+		?	?	Very strong movements of the arms on weak current	?	
26.	Encephalitis (chronic)	7/3	1?– 13	50	0.045	+			?	?	Immediately lets go of the electrodes on weak current	?	
27.	Chorea (chronic)	0/3	0 – 8	58	0.026			+	+				+
28.	Encephalitis? tumor cerebri?	3/3	0 – 7	65	0.007		+			+			+
29.	Encephalitis; glycosuria renalis	0/3	2 – 22	79	0.008		+			+			+
30.	Tumor reg. chiasmatic	0/3	6 – 90	81	0.000		+			+			+
31.	Chorea (chronic) hereditary	0/3	0 – 14	51	0.018			+	+				+
32.	Wilson's disease	2/3	0 – 12	51	0.018			+	+				+
33.	Monoparesis; hysteria	6/3	1 – 14	68	0.036	+				+			+
34.	Paralysis agitans	1/3	2 – 18	56	0.018			+	Not examined				

As regards these last cases (Nos. 23, 24, 25, 26) the B.F.I. reactions observed were of such a kind that so far they must be called "functional," whereas the A.L.S.R. showed definite divergence from the normal.

While one would be most inclined to look upon an abnormal A.L.S.R. as a symptom of organic disease, the B.F.I. reactions which have so far been grouped as "functional" are not yet clearly defined. Among other things the location of the affection plays a part, and also the reciprocal collaboration of the cortex and the striatum in each given case.

In the 7 cases in which the disagreement was evident the grouping according to the nature of the symptoms is of some interest.

Without considering the central localization of these two reactions, a subject about which we know nothing, we are justified in supposing that the A.L.S.R. is released by vegetative functions, while the B.F.I. is released *via* motor centers. In 3 of the disagreeing cases the clinical symptoms were essentially of a motor nature (Nos. 27, 31, 32). Here we found a normal A.L.S.R. but an atypical B.F.I.

In 2 other cases of this group (Nos. 29, 30), in which vegetative symptoms were the essential ones, the results were just the reverse. On the whole, atrophy of the striatum seems often to show normal A.L.S.R., at any rate in the first stages. In this respect the 3 cases of paralysis agitans, which have been examined by both methods, are interesting (Nos. 17, 18, 19). The abiotrophy seems so selective in these cases that neither the vegetative functions nor the striatal tracts of the arm reflexes are disturbed by the morbid processes, as in these patients we found normal A.L.S.R. as well as B.F.I. (No. 34, A.L.S.R., normal). On the other hand, in postencephalitic cases of Parkinsonism an abnormal result of both the reactions seems to be the rule, probably because the inflammatory process attacks in the brain tissue far more diffusely than does the abiotrophy. This, moreover, speaks in support of the opinion stated by Viggo Christiansen at the Neurologic Congress in 1920 in Paris—that postencephalitic Parkinsonism and that of paralysis agitans are two quite separate morbid units.

Last, Case 7 is of special interest. In this patient, who suffered from a cervical spondylitis with radicular symptoms, there were no clinical signs of an affection of the striatum. The decrease in the A.L.S.R. and the atypical B.F.I., which quite unexpectedly were found in this case, are therefore instructive in several respects. In the first place, the uniform result of the reactions in this concrete example illustrates the support which mutual agreement means to the judgment of the value of each single method. Even though it is not the rule that abnormal reactions are found in cases of affections of the spine or in juxtaspinal affections, a finding like the one mentioned will nevertheless cause doubt as to the utility of a single

method. It is another matter when two different methods both show results which point in the same direction. In the second place, we see how the methods, alone, or especially when combined, may give us information of an affection of the striatum, which we are not able to recognize with the clinical examination alone. In the third place, these circumstances show us a use of the methods beyond the purely diagnostic one. Granted that these two methods are taken up for clinical use, the possibility appears of an investigation of a more theoretical kind of different groups of diseases, not only in neurology and psychiatry, but also in different types of diseases belonging to other phases of medicine. For, by these methods it may be possible to determine the presence of a striatal component in a given facies morbi.

Considering the importance of the striatal part of the brain in numerous pathologic conditions, circumstances which are as yet not very clear, valid examinations of this kind may be said to be of importance.

Summary. A comparison of the Munch-Petersen and Wernøe tests of function of the corpus striatum has been made in 33 cases. In 22 cases the tests showed good agreement; in 4 circumstances prevented a comparison and in 7 the results were not in agreement. The nature of the disagreement in the last group is discussed and the value of the use of both tests emphasized in giving information about possible lesions of the corpus striatum.

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A COMBINED NEEDLE AND CANNULA FOR THE ADMINISTRATION OF TRANSFUSIONS, AND INTRAVENOUS AND SUBCUTANEOUS INFUSIONS.

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In medical and surgical practice the occasion to perform transfusions or to administer fluids subcutaneously or intravenously over prolonged periods of time frequently arises. The various types of rigid sharp-pointed steel needles which are commonly employed in these procedures have the great disadvantage that inadvertant motion on the part of the patient when the needles are *in situ* may cause local trauma and often pain. When a patient who is receiving intravenous therapy becomes restless or uncoöperative the needle is

often displaced from the vein or may have its point forced through the wall of the vessel. The inevitable result of either of these accidents is the occurrence of perivenous hemorrhage and infiltration, which often is not only painful but may also occasionally result in local tissue necrosis if certain solutions are employed. In those instances in which it is necessary to expose the vein surgically and fix a rigid metal cannula in place, the same dangers exist. In an effort to prevent these unfortunate occurrences, after the needle or cannula has been introduced, the patient's extremity frequently is fixed in an immobilizing device such as a splint. Thus, because of certain undesirable features inherent in the conventional instruments, lacking more perfect equipment we are forced to add to the discomfort of patients already ill.

In an effort to obviate the disadvantageous features of the hypodermoclysis and the intravenous needle, as well as the intravenous cannula, we planned to supplant these three by a single new instrument which we felt should possess the following qualities: (1) It should not have a sharp point capable of traumatizing the vessel wall or causing penetration as a result of motion on the part of the patient. (2) It should be flexible for the same reason. (3) It should not be readily displaceable. (4) It should lend itself readily to introduction subcutaneously and to introduction intravenously, by venipuncture or surgical exposure. (5) It should resemble the conventional instruments, so that any one accustomed to their use would be able to employ it readily, without the necessity of adopting a new or complicated technique.

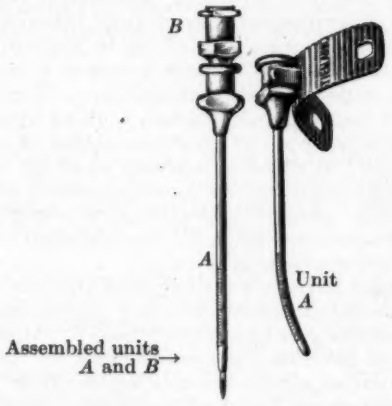
With these objects in view, we have devised an instrument which fulfills the necessary requirements and which in actual practice has proven satisfactory. It consists of two parts, which we shall arbitrarily designate as Unit A and Unit B. Unit A represents the true instrument, while Unit B is employed merely to facilitate the introduction of the former.

Unit A resembles somewhat an ordinary No. 12 gauge intravenous needle with a shaft 2 inches long. The proximal $1\frac{1}{4}$ inches of the shaft is rigid and ends in a hub which fits a Luer syringe. The distal $\frac{3}{4}$ inch of the shaft, however, is flexible and is so constructed of fine, closely-coiled silver wire that it can readily be bent even on slight pressure. The tip of the instrument instead of being sharp and bevelled is blunt and rounded.

Within the lumen of Unit A there snugly fits a conventional No. 20 gauge sharp-pointed, rigid Luer needle which we have designated as Unit B. When the two units are assembled this second needle (Unit B) is sufficiently long to project for a short distance beyond the tip of Unit A. The two units fit one another accurately, so that no special locking device is needed. The purpose of Unit B is as follows: (1) To act as a stylette, in order to render the instrument rigid during introduction into a vein or beneath the skin. (2) To supply a sharp point to the instrument,

in order to facilitate its introduction. (3) To enable one to draw blood with a syringe from the vein, while introducing the instrument by puncture, and thus to make certain that it has been accurately introduced.

After the assembled instrument has been introduced, the inner rigid needle (Unit B) is withdrawn leaving only the outer flexible needle (Unit A) *in situ*. The instrument should always be introduced for a distance of at least 1 inch, so as to prevent leakage which may sometimes occur through the interstices of the distal, flexible ¾-inch segment, if motion on the part of the patient should accidentally acutely angulate it. When employing the instrument for hypodermoclysis or intravenous infusion by puncture, it must be introduced with both units assembled, for the reasons stated above. On the other hand, when employing it for intravenous infusion by surgical exposure of the vein it is necessary to introduce



Unit A only. After introduction, fixation *in situ* is facilitated by means of a readily applicable snap clip which grasps the hub and which presents two lateral wings of flexible metal for broad approximation to the skin by means of a tape or adhesive straps.

In actual practice the instrument possesses the following attributes: (1) It may be used for transfusion, hypodermoclysis or for venoclysis, by puncture or surgical exposure. (2) It is less apt than the conventional type of needle to cause trauma or penetration of the vessel wall, with resultant perivenous hemorrhage and infiltration. This is so because of its flexibility and the fact that it bears a blunt rounded point. (3) It is not as readily displaceable as the conventional type of needle, because the ribbed outer surface of the distal flexible segment tends to prevent accidental slipping. (4) Its mode of introduction differs in no respect from that of the conventional types of needle or cannula.

NOTE.—This needle is manufactured by George Tiemann & Co., New York City.

REVIEWS.

HUMAN CANCER. By ARTHUR PURDY STOUT, M.D., Associate Professor of Surgery, College of Physicians and Surgeons, Columbia University; Attending Surgical Pathologist, Presbyterian Hospital, New York. Pp. 1007; 331 illustrations. Philadelphia: Lea & Febiger, 1932. Price, $10.00.

"THIS monograph . . . is an attempt to discuss the development and growth of all of the different kinds of cancer in the human body. It has long been recognized that each particular anatomical region of the body produces cases which differ in many respects from those in other parts of the body. Therefore this book deals with cancer by regions. Although not universally accepted, the idea that chronic irritation is an important factor in etiology enjoys a wide popularity at this time. For clarity and convenience in discussion it has been accepted as a working hypothesis, the description of every cancer is preceded by a section labeled 'etiological factors and precancerous lesions,' in which is collected all of the information which could be found bearing upon the relationship between the action of the so-called 'chronic irritants' cellular hyperplasias including benign neoplasms, and cancer. The reader must judge whether sufficient evidence has been offered to make this hypothesis tenable or not.

"No attempt has been made to discuss the chemical aspect of neoplasms, the biological differences between cancer cells and normal cells and the biochemical effects of cancerous growth upon the body." Most phases of experimental cancer research have also been omitted.

In the introduction certain important matters are carefully considered. For example, under "Precancerous Lesions," the author says, "In some ways this has been an unfortunate term because it has connoted in many minds the *inevitable* sequence of events. Such, of course, is very far from the truth; if it were true, the human race would long ago have become extinct. . . . By precancerous, therefore, is meant simply a condition which may be associated with the development of cancer."

Another point discussed is the "Criteria of Cancer" upon which there is such uncertainty today that one pathologist considers a tumor malignant which another calls benign. In order that there shall be no misunderstanding of what the author thinks, he generalizes thus: "A cellular proliferation is probably not a cancer, unless one finds *both* the morphological changes of the individual cells which are found in undoubted cancers and also evidences of infiltrative growth outside of the usual anatomical boundaries of whatever type of cell happens to be under consideration."

With this interesting beginning the real book begins with "The Oral Cavity," and here the heart of the Reviewer fails him, for a definite program for arranging the text now appears. We find that the oral cavity consists of the lips, tongue, floor of the mouth, cheeks, gums of the mandible, upper oral cavity and posterior oral cavity, for each of which all of the possible tumors are to be considered with reference to etiology, spread, symptoms, diagnosis, prognosis, treatment. Then follows the same for the dental apparatus, the salivary glands, the esophagus, the stomach, the liver and

intrahepatic bile passages, the gall bladder and extrahepatic ducts, the pancreas and ampulla of Vater, the intestine and rectum, the appendix, the peritoneum, omentum, mesentery and retroperitoneal tissues. This occupies 248 pages, to be followed by similar treatment of the mammary gland, the uterus, the vulva and vagina, the female urethra, etc.

Such an arrangement makes the work a book of reference, and as such it is excellent and very useful, but it almost destroys its readability.

Both author and publisher are to be congratulated in having produced a handsome, beautifully illustrated and highly useful book along lines that are unconventional. J. McF.

LIVING THE LIVER DIET. By ELMER A. MINER, M.D., Independence, Kan. With an Introduction by WILLIAM P. MURPHY, M.D., Instructor in Medicine at the Harvard Medical School, Boston. Pp. 108; 3 illustrations. St. Louis: The C. V. Mosby Company, 1931. Price, $1.50.

A LITTLE diet manual for the pernicious anemia patient which will find its chief value in the numerous recipes and in the enthusiastic manner of presentation by the author, himself afflicted with the disease. R. K.

OSLER AND OTHER PAPERS. By WILLIAM SYDNEY THAYER, M.D., LL.D., DR. HON., SC.D., F.R.C.P. (IRE.) HON., Professor Emeritus of Medicine at The Johns Hopkins University. Pp. 386. Baltimore: The Johns Hopkins Press, 1931. Price, $3.50.

ONE of Osler's greatest attributes was unquestionably his ability to harmonize groups in which he was active and to stimulate younger men to enthusiastic, constructive work. It is fitting that one who gratefully acknowledges his great debt should produce this volume, which is in part at least a notable tribute to "the Chief." But it is even more valuable as a collection—incomplete, unfortunately—of writings of one of the most charming medical essayists of our time. One does not have to read many pages before appreciating what a trenchant evaluation with illuminating sidelights this is of a great medical figure that none but the author could have given. Still more is one eventually impressed by the fact that the clear graceful periods are conveying *tute et jucunde* invaluable maxims to students of medicine and to the medical profession at large. If our profession in this country could be more under the guidance of such pure-minded, penetrating artists, there would be less call for wringing of medical hands, advice of often self-appointed efficiency experts, and the expensive fact-finding of investigating committees. As in the author's quotation from Monna Vanna, "Each man sees in another individual that which he sees in himself and each one comprehends the other individual in a different fashion and precisely from the level of his own moral nature;" so too the reader learns much about the writer as he proceeds.

Of the 24 essays, the first 15 are directly connected with Osler; numbers 7, 8, 14, 15, 16, 20 and 22 are inspiring addresses to boys of all ages, chiefly medical; while Cotton Mather, Laennec, Bright, Fitz, Welch and Howland are subjects of semibiographical sketches. But why attempt vivisection of a living unit? The book can be read from cover to cover, as I did, or any of its component parts may be selected, and with either method pleasure and profit are guaranteed. E. K.

A Doctor of the 1870's and 80's. By William Allen Pusey, Sometime President of the American Medical Association and of the American Dermatological Association. Pp. 153; illustrated. Springfield, Illinois: Charles C Thomas, 1932. Price, $3.00.

Although writing the biography of the father for whom one had a "boundless respect and affection" may be as difficult as achieving an accurate autobiography, in the present case success has been accomplished. The author not only tells an interesting story sympathetically but obviously has accurately portrayed the daily existence of a flourishing country doctor in an average rural community of the previous generation but of an age that has passed. Before bacteriology had had time greatly to influence medicine and surgery (and the elder Pusey is admitted not to have grasped its significance) and before the telephone and automobile had revolutionized country practice, this austere, wise, keen and courageous practitioner took adequate care of the health of his community and lived a full life of the kind that has contributed so largely to making our nation what it is. As a counterfoil to the unrealities of the country doctor of fiction, this figure contributes an historical record of value. E. K.

Conquering Arthritis. By H. M. Margolis, M.D. Pp. 188; 2 illustrations. New York: The Macmillan Company, 1931. Price, $2.00.

The author has attempted a difficult thing and can hardly be said to have succeeded. The first 120 pages take up the question of classification of the chronic arthritides and a description of rheumatic fever. In this description of the varieties of arthritis which is a departure from accepted classifications, gout, a condition admittedly uncommon in America at least, occupies 12 pages. Atrophic arthritis is inadequately designated "infectious" arthritis. The author devotes several pages to the influence of sympathectomy on the condition, avowedly a measure of last resort. The sections on blood chemistry and on the bowel in arthritis show only a superficial acquaintance with the literature on these subjects. The sections on nonspecific protein and vaccine are very well done. The diet recommended in "infectious" arthritis is high in calories and unrestricted in other respects: this is not a reflection of the opinion of the best authorities. The book is somewhat verbose and filled with rather loose optimism. On the whole the patient who trusts to this book will not be safely guided through the mazes of arthritis. E. P.

Practical Morbid Histology. By Robert Donaldson, M.A., M.D., Ch.B. (Edin.), F.R.C.S.E., D.P.H., Sir William Dunn Professor of Pathology in the University of London, etc. With Foreword by Sir Humphry Rolleston, Bart., G.C.V.O., K.C.B., M.D., Regius Professor of Physics, University of Cambridge. Pp. 487; 214 illustrations. Second Edition. St. Louis: The C. V. Mosby Company, 1931.

"With the ever-expanding scope of pathological science, the attractions of bacteriology, immunology and biochemistry, and the increasing demands on the time of the hard-worked medical student, there has arisen a real danger that changes in structure, as seen with the naked eye in the postmortem room and under the microscope in the laboratory, which are so inseparably bound up with functional reactions, or symptoms, may receive insufficient attention. A practical knowledge of morbid anatomy is an essential basis for the understanding and interpretation of the physical signs of disease,

and so for a correct diagnosis, and also in connection with the further and more difficult problem of prognosis. Experience gained in the postmortem room of what are the common pathological changes engenders a sense of due proportion in estimating the character, extent and associations of structural changes in a given case, and such a training checks fanciful guesses and hypothetical diagnoses. Neglect of the study of structural change may naturally result from realization of the importance of recognizing and investigating the earliest departures from the normal and functional disorders; this tendency should be corrected by Professor R. Donaldson's clear account of the morbid changes of structure in this enlarged second edition enhanced in value by numerous illustrations."

(Extract from Sir Humphry Rolleston's Foreword.)

PRACTICAL ENDOCRINOLOGY. By HENRY R. HARROWER, M.D. Pp. 704. Glendale, California: Pioneer Printing Company, 1931. Price, $5.00.

As a reference book (for which it is primarily intended) and used in the right way, this book should prove extremely useful in a field, which though often cultivated by methods of dubious value, is admittedly of the very greatest importance. The author's familiarity with the subject is evinced in an interesting 20-page chronological list of "endocrine events;" and yet this also brings out a weakness of the literature in this field in that it records a number of discoveries of doubtful or even rejected value. Under the four headings of Fundamentals, Principles, Diagnostics and Therapeutics, the actions of some 16 organs are considered as applied to a wide range of human ills. In the section on the stomach of the chapter on Principles, such preparations as gastron, gastrin, myogestin and ventriculin are considered; while under the spleen we read of lienin, stagnin, hormonal, colloidogenin, splenocrin and other little known substances. From one point of view this may be looked on as adding to the value of the work as a reference book. Considerably more than half the book is devoted to therapeutic considerations. E. K.

THE VITAMINS. Monograph of the Pickett-Thomson Research Laboratory, Vol. I, September, 1931. By ETHEL BROWNING, M.D., Liverpool, Assistant Pathologist to the Pickett-Thomson Research Laboratory, St. Paul's Hospital, London. Pp. 575; illustrated with figures and tables. London: Bailliere, Tindall & Cox. In America, Baltimore: The Williams & Wilkins Company, 1931.

THIS book is a very complete compilation of the material on the vitamins. One especially commendable feature is the emphasis laid upon the pathological lesions associated with the avitaminoses. It is to be regretted, however, that with a wealth of material from which to select illustrations of the histopathology, so much space should be given to lesions produced by "bad diets" and relatively so little to specific changes. E. W.

COURTS AND DOCTORS. By LLOYD PAUL STRYKER. Pp. 236. New York: The Macmillan Company, 1932. Price, $2.00.

MR. STRYKER, having been for many years general counsel for the Medical Society of the State of New York, is well prepared to write a book of this kind. The book itself is a much needed guide for physicians in their

relation to the law—their duties and rights as citizens. Government has become so paternal and bureaucratic that physicians, and indeed all citizens who engage in any business or profession must know much more about legal matters than formerly in order to keep out of trouble.

The changed attitude of the people about the function of government has led to evil, not to good. The founders of the Republic regarded government simply as a necessary evil and hence they restricted its duties merely to police work and taxation. The newer attitude, that people are made for the state, that the state is to be a nursing mother, to "give buns to the people who have no teeth," to make an environment for the unfit at the expense of the fit, to make them happy, has made life so complicated and laws so multitudinous that no physician can live today without employing a lawyer to look after his interests. Blackmail, malpractice suits, the narcotic and prohibition laws, and the bureaucratic attitude of government officials make a book like this necessary for every physician. C. B.

HISTORY OF MEDICINE IN THE PROVINCE OF QUEBEC. By MAUDE E. ABBOTT, B.A., M.D. Pp. 97; 41 illustrations. Montreal: Medical Museum, McGill University, 1931. Price, $3.00.

THIS outline of Quebec medicine is reprinted with additions from "The Storied Province of Quebec." The first half tells of primitive Canadian medicine, the struggles of the early French colonists, and the rise of the French hospitals from a different point of view, to be sure, but in considerably less detail than does Heagerty's "Four Centuries of Medical History in Canada" (see review in *Am. J. Med. Sci.*, 1929, **178**, 270). The latter half, especially those pages dealing with the Montreal General Hospital and McGill University and the present situation, progresses more firmly and entertainingly. The paper and some of the illustrations are regrettably poor; yet we recommend the reading matter highly to those interested in the subject. E. K.

HERZ UND ANGST. By PROF. DR. LUDWIG BRAUN. Pp. 119. Wien Franz Deuticke, 1932. Price, M. 6.—.

A CONTINUATION of *Herz und Psyche*, published by the author in 1920, this essay, based on observation of the sick, analyzes "anxiety" (Angst) from the etymologic, clinical, physiologic, diagnostic and phylogenetic points of view. Committed to the theory that the sensation of anxiety is a specific sensation of the heart, it finds copious support in literature and ancient science even before Aristotle's enunciation that the heart was the seat of the mind. In modern times fewer quotations are available. The author is content with such assertions as that we may remain quiet in the face of great emotion or danger, until suddenly we are overcome with anxiety due to the occurrence of abnormal sensations in the heart.

E. K.

FEMALE SEX HORMONOLOGY. By WILLIAM P. GRAVES, A.B., M.D., F.A.C.S., Professor of Gynecology at Harvard Medical School; Surgeon-in-Chief to the Free Hospital for Women and to the Parkway Hospital, Brookline. Pp. 131. Philadelphia: W. B. Saunders Company, 1931. Price, $3.50.

THIS book consists of a review of the enormous amount of work which has been done in isolating and evaluating the various female sex hormones,

bringing together in one small volume a well-digested summary of our present knowledge of this complex subject. Since these studies have introduced into medical literature a host of new words, the inclusion of a glossary which well defines them is a most welcome item and for those who wish to go further into the subject an excellent bibliography is appended. Organotherapy is considered purely from the scientific aspect in a most conservative manner, with no specific recommendations as to dosage or product, but rather indicating the limitations of such therapy at the present time. Some of the contained information may be of little value a few years hence, since this subject is in the formative period, nevertheless it is an excellent résumé and is of the same standard as the author's literary contributions. F. B.

NUTRITION ABSTRACTS AND REVIEWS. VOL. I, NOS. 1 and 2. October, 1931. Issued under the direction of the Imperial Agricultural Bureau, the Medical Research Council and the Reid Library. Pp. 351. Aberdeen: The Aberdeen University Press, Ltd., 1931. Price, 13s.

THIS Journal has as its editors the well-known scientists, John Boyd Orr, J. J. R. Macleod, Harriette Chick and corresponding editors from centers throughout the world. Its purpose is to collect abstracts of all literature bearing on nutrition of man and of farm animals. More than 450 journals are reviewed. A number will deal with the present state of knowledge of different aspects of the subject, giving a bibliography of the literature. Others will be devoted to articles of a more general nature stating a point of view. There are also book reviews.

The abstracts are arranged under the following headings: Technique; composition of foodstuffs; physiology of nutrition; dietetics; feeding of animals; diet in relation to health and disease. There is an author's index and also an index of the contents.

The abstracts in the present number are concise and give the essential facts of the articles reviewed. Each abstract has the title in the native language and if foreign, an English translation, the number of references, graphs, illustrations and the institution from which it comes. In view of the rapidly increasing literature in this field, the journal should be a great aid to those interested in the subject.

The annual price is 21 shillings. However, no mention is made of the number of issues per year. L. J.

GROWTH IN PRIVATE SCHOOL CHILDREN. By HORACE GRAY, Stanford University Hospital, San Francisco, and J. G. AYRES, The Institute for Juvenile Research and Behavior Research Fund, Chicago. Pp. 282; illustrated with figures and tables. Chicago: University of Chicago Press, 1931. Price, $3.50.

FUNDAMENTALLY this book presents the carefully compiled results of 4583 sets of measurements (3110 of boys and 1473 of girls) of private school children, classified by age groups from 1 to 19 years. The set includes weight, 17 linear measurements, 17 indices related to stature and 8 other indices. Standard deviations and coefficients of variation are given for each of the 43 items by sex and age group.

The material affords basal data which the pediatrician versed in the terminology of elementary statistics can readily use in estimating the development of a child in his care. To the young contemporary worker

in this field the chapters on anthropologic and statistical method, on body types, on sexual, racial, age and economic differences will be found most instructive and the bibliography most useful. Above all, the book is a record of anthropologic research and observation which will one day be an historical document.

In the chapter on Race the author, judging by the percentage of replies received in response to his short questionnaire, concludes that the East is third and last in showing interest in schools and children. Due to a discrepancy between table and text, it is not clear whether it is Chicago or California which leads.

C. M.

A Description of the Planes of Fascia of the Human Body. By B. B. Gallaudet, M.D., Department of Anatomy, College of Physicians and Surgeons, Columbia University, New York. Pp. 75. New York: Columbia University Press, 1931. Price, $2.00.

This small volume represents the results of an intensive study of the fascias of the human body, by a highly trained anatomist of many years' experience in the dissecting room. The main thesis is that the fascial planes constitute a continuous sheet of connective tissue, varying in thickness and density according to location. The numerous separately named fascias of the textbooks are all discussed, and comparisons are made with the author's observations in 34 bodies, dissected solely for this study. Special attention is paid to the fascial planes of the abdomen, pelvis and perineum, and critical descriptions of these are given.

W. A.

The Renal Lesion in Bright's Disease. By Thomas Addis, Professor of Medicine, Stanford University, and Jean Oliver, Professor of Pathology, Long Island College of Medicine, Formerly Professor of Pathology, Stanford University. Pp. 628; 170 full page plates, 2 in color; 21 illustrations and 1 folding table. New York: Paul B. Hoeber, Inc., 1931. Price, $16.00.

This splendid book is the coöperative work of a clinician and a pathologist, both well known students of Bright's disease. It is not a mere review of the literature but rather an account of the personal studies of the authors. The chief aim is correlation between clinical and morphologic facts, that is to say between carefully studied functional and structural disturbances. For too long a time have pathologic physiology and pathologic anatomy been divorced, to the great harm of either discipline. In this book, as in the great work by Volhard and Fahr on renal disease, the functional and structural changes are successfully regarded not as separate subjects but as integral interrelated parts of Bright's disease. The authors point out that Bright himself stressed that disease must be interpreted by "A reference to morbid anatomy." With this aim in view the authors present a very careful analysis of about 100 cases, all of them personally investigated by methods designed to permit correlation between the clinical and the morphologic observations. There is given an excellent description of the clinical methods elaborated to determine the degree of renal function, and the nature and extent of the renal lesions. Similarly, the purpose and the technique of the pathologic methods are clearly presented, and the meaning of the clinical and pathologic terms employed are rigidly defined. A very valuable part of the work is the complete presentation of many case reports. The structural changes are beautifully illustrated by micro-

photographs. There are chapters on the classification and theory of Bright's disease, and on the course and sequence of the pathologic processes in this disease.

The work can highly be recommended to physicians and pathologists who desire a thoroughly modern presentation of Bright's disease.

B. L.

PHANTASTICA, NARCOTIC AND STIMULATING DRUGS. By LOUIS LEWIN. Pp. 335. New York: E. P. Dutton & Co., 1931. Price, $3.75.

THIS volume, the first of its kind, tells in a fascinating way of the drugs and substances that man—civilized and savage—seems always to have used to soften his sorrows and to add to his pleasures.

Comprehensive consideration is here given of narcotic and stimulating drugs which are classified as follows: (1) Euphorica: substances which inhibit the functions of emotion and perception, giving physical and mental comfort, including morphin, cocain, etc. (2) Phantastica: cerebral excitants that bring about hallucinations and illusions; mescal buttons and Indian hemp represent the series. (3) Inebriata: such as alcohol, chloroform, ether and benzin, which primarily cause cerebral excitation later to be followed by depression or possibly by cessation of function. (4) Hypnotica: somnolent substances, such as chloral, veronal and sulphonal. (5) Excitanta: mental stimulants which do not cause a change in consciousness; these are vegetable substances like caffein, tobacco and betel.

The soul is mentioned with recurring frequency—13 times. Is this unlucky for science, for metaphysics or for neither? There is a tone of pessimism in the book which is a bit disturbing; doubtless the use of narcotic substances is increasing absolutely but perhaps not so much relatively. This is a world of change and there is easily a chance of a change for the better.

N. Y.

BOOKS RECEIVED.

NEW BOOKS.

The Sign of Babinski. By JOHN F. FULTON, Sterling Professor of Physiology in the Yale University School of Medicine, and ALLEN D. KELLER, Professor of Physiology and Pharmacology in the School of Medicine, University of Alabama. Pp. 165; 65 illustrations. Springfield, Illinois: Charles C Thomas, 1932. Price, $5.00.

Individuality of the Blood. By PROF. LEONE LATTES, Director of the Institute of Forensic Medicine in the University of Modena. Translated by L. W. HOWARD BERTIE, M.A., B.M., B.CH. (OXON.), from the French edition 1929. Pp. 413; 71 illustrations. New York: Oxford University Press, 1932. Price, $7.50.

Diabetes in Childhood and Adolescence. By PRISCILLA WHITE, M.D., Physician at the New England Deaconess Hospital, Boston. With a Foreword by ELLIOTT P. JOSLIN, M.D., Clinical Professor of Medicine, Harvard Medical School; Consulting Physician, Boston City Hospital. Pp. 236; 25 illustrations, 1 colored plate. Philadelphia: Lea & Febiger, 1932. Price, $3.75.

The Use of Lipiodol. By J. A. SICARD, Late Professor in the Faculty of Medicine, Paris, and Physician at the Necker Hospital, and J. FORESTIER (Aix-les-Bains). Pp. 235; 50 illustrations. New York: Oxford University Press, 1932. Price, $4.00.

The Medical Annual 1932. Jubilee Volume, 50th Year. By various contributors. Edited by CAREY F. COOMBS, M.D., F.R.C.P., and A. RENDLE SHORT, M.D., B.S., B.Sc., F.R.C.S. Pp. 674; 179 text illustrations and 81 plates, plain and colored. Bristol: John Wright & Sons, Ltd., 1932. Price, 20/– net. American publisher: William Wood & Co., Baltimore. Price, $6.00.

International Studies. Medicine and the State. Conducted for the Milbank Memorial Fund. By SIR ARTHUR NEWSHOLME, K.C.B., M.D., F.R.C.P. With a Foreword by WILLIAM H. WELCH, M.D., LL.D. Pp. 300. Baltimore: The Williams & Wilkins Company, 1932.

The Nature of Disease Journal, Vol. I. By J. E. R. MCDONAGH, F.R.C.S. Pp. 171. London: William Heinemann, Ltd., 1932. Price, 7/6 net.

Accidents, Neuroses and Compensation. By JAMES H. HUDDLESON, M.D., Associate in Neurology, Columbia University; Attending Neurologist, Neurological Institute, New York. With a Foreword by J. RAMSAY HUNT, M.D., Sc.D., Professor of Neurology, Columbia University. Pp. 256. Baltimore: The Williams & Wilkins Company, 1932. Price, $5.00.

International Studies. Prevention and Treatment of Disease, Vol. III. England and Wales, Scotland and Ireland. Conducted for the Milbank Memorial Fund. By SIR ARTHUR NEWSHOLME, K.C.B., M.D., F.R.C.P. Pp. 558; illustrated with tables. Baltimore: The Williams & Wilkins Company, 1932. Price, 16s.

The Medical Clinics of North America, Vol. 16, No. 1 (Philadelphia Number, July, 1932). Pp. 290; 75 illustrations. Philadelphia: W. B. Saunders Company, 1932. Price, Paper $12; Cloth $16.

Nosokomeion. Quarterly Hospital Review. Second Special Number, containing the proceedings of the Second International Hospital Congress. Pp. 313. Stuttgart: W. Kohlhammer, 1932. Price, 11.25 Marks.

Quantitative Clinical Chemistry, Vol. 2, Methods. By JOHN P. PETERS, M.D., M.A., Professor of Internal Medicine, Yale University, School of Medicine, and DONALD D. VAN SLYKE, PH.D., Sc.D., Member of The Rockefeller Institute for Medical Research. Pp. 957; 95 illustrations. Baltimore: The Williams & Wilkins Company, 1932. Price, $10.00.

NEW EDITIONS.

The Chemistry of Tuberculosis. By H. GIDEON WELLS, M.D., PH.D., Director of the Otho S. A. Sprague Memorial Institute, and Professor of Pathology in the University of Chicago, and ESMOND R. LONG, M.D., PH.D., Director of the Laboratory of The Henry Phipps Institute for the Study, Treatment and Prevention of Tuberculosis, and Professor of Pathology, University of Pennsylvania, formerly Professor of Pathology in the University of Chicago. Pp. 481; illustrated with tables. Second edition, thoroughly revised. Baltimore: The Williams & Wilkins Company, 1932. Price, $7.00.

Manuale di Analisi Chimica. By CESARE SERONO, Dottore in Medicina ed in Chimica; Docente in Chimica e Microscopia Clinica Nella R. Università di Roma. In collaboration with PROF. ALFONSO CRUTO. Pp. 483; 85 illustrations. Second edition. Torino: Unione Tipografico-Editrice Torinese, 1932.

The Anatomy of the Human Orbit. By S. ERNEST WHITNALL, M.A., M.D., B.CH. (OXON.), M.R.C.S., L.R.C.P. (LOND.), Professor of Anatomy, McGill University, Montreal. Pp. 467; 212 illustrations. Second edition. New York: Oxford University Press, 1932. Price, $6.25.

PROGRESS
OF
MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

W. S. THAYER, M.D.,

PROFESSOR OF MEDICINE, JOHNS HOPKINS UNIVERSITY, BALTIMORE, MARYLAND,

AND

JOHN H. MUSSER, M.D.,

PROFESSOR OF MEDICINE, TULANE UNIVERSITY OF LOUISIANA, NEW ORLEANS.

Arterial Atony and Arteriosclerosis.—PLESCH, Professor of Internal Medicine in the University of Berlin (*Lancet*, February 20, 1932, p. 385) advances the thesis that arteriosclerosis is only a part of a general constitutional systemic disease which affects particularly unstriped muscle and attaching the whole vascular system simultaneously. It is a disease which sets in at a comparatively early age, which can be arrested and cured in the early stages, according to Plesch's ideas, and in which the local arteriosclerotic changes such as calcification, represents purely a defensive mechanism. The arteriosclerosis of old age due to wear and tear shows local calcified areas, whereas arteriosclerosis is a disease which at the onset at least involves simultaneously and equally the entire vascular tree. That these two types differ clinically is a well known observation. The primary etiologic factor responsible for true arteriosclerosis is a weakening of the muscular and elastic elements of the blood vascular walls. They become stretched and dilated at such points that are exposed to dynamic pressure so that histologic changes occur, serving to raise the resistance of the walls. This pathologic change is ultimately completed by the deposition of lime plates so that calcification and ossification of the vessel represents not another disease but a healing process. Plesch's ideas are substantiated by certain pathologic-anatomic observations and by certain etiologic, statistical, experimental and clinical proofs. It would be impossible to detail all these data that Plesch has given to maintain his thesis. Certainly if they are taken individually and collectively they represent a large group of phenomena which might explain the occurrence of arteriosclerosis as a disease which depends primarily upon atony of the arteries. Although it is possible to view with acquiescing interest the ideas Plesch has concerning the mechanism of the production of arteriosclerosis it is however difficult to accept, except with a certain amount of skepticism, his ideas concerning therapeusis and the cure of arteriosclerosis. He suggests for treatment, among other things, blood letting at times; the reduction of nitrogen and salt in the diet; rest in the horizontal position thereby relieving the heart, in order to exclude the hydrostatic pressure factor which is an important part of the pathologic

mechanism; a "dietetic day" once a week; and much fresh air. Particularly stimulating is his idea that the majority of cases can be handled without the use of drugs. Digitalis he says is objectionable; cardiac tonics not indicated. Small doses of iodid of potassium are injurious rather than useful. Most drugs that directly affect the vessels are harmful. His one therapeutic suggestion is when arteriocapillary fibrosis has already developed iodid of potassium in doses up to 8 gm. daily should be ordered for 10 days disregarding any symptoms of iodism.

SURGERY

UNDER THE CHARGE OF
T. TURNER THOMAS, M.D.,
PHILADELPHIA, PA.

The Treatment of Syphilis.—GOUIN, BIENVENUE and DAOOLAS (*Urol. and Cutaneous Rev.*, 1931, **25**, 770) say that the application of the leukocyto-reaction is indicated as a means of diagnosis in suspected syphilis where the serologic reactions are mute and the clinical evidences doubtful. The leukocyto-reaction will also be indicated for gauging from time to time the drug used. The reactions of the body against the disease, or the drugs, change in effect either spontaneously or by the evolution of the disease or by treatment. All syphilologists know the variations of resistance of syphilis, the variations in the action of a drug in a given subject, as well as the variations in tolerance. If one only utilizes the adequate drug one will avoid bad or useless treatments or a mixed series used blindly. Finally the leukocyto-reaction will be indicated for determining the termination of antisyphilitic treatment, that is to say, if the patient is cured and to test this cure by different salts. A leukocyto-reaction remaining positive demonstrates the necessity of continuing intermittent treatment.

Interparietal Hernias.—LOWER and HICKEN (*Ann. Surg.*, 1931, **94**, 1070) claim that interparietal hernia is a term used to designate a group of hernias which occur in the inguinal region between the various layers of the abdominal muscles and are classified according to the anatomic location of the hernial sac. Properitoneal hernia includes all those cases in which the hernial sac lies between the peritoneum and the transversalis fascia, 119 such cases being reported. In the interstitial hernia the sac lies between the transversalis fascia and muscles between the transversalis and internal oblique muscles or between the two oblique muscles, 348 such hernias having been reported. In superficial hernia the sac may be monolocular or multilocular, the latter being the form present in the majority of cases. The usual clinical picture is that of intestinal obstruction. Treatment consists of early recognition and immediate relief by operation.

Suprapubic Prostatectomy.—LONSLEY and KERWIN (*J. Am. Med. Assn.*, 1932, **97**, 1669) believe that the surgeon operating on the prostate must adopt the procedure employed to the special needs of the patient

involved; there can be no routine technique applicable to all cases. Suprapubic prostatectomy is a one-man operation, while perineal prostatectomy requires coöperation of a trained team. If the prostatic hypertrophy has dilated the internal sphincter, enucleation of the gland is better done by the suprapubic route. When the enlarged gland has remained within its natural anatomic limits it can be reached more safely and conveniently by way of the perineum. The authors prefer the technique of suprapubic prostatectomy devised by Freyer more than 30 years ago, whose procedure consisted of enucleation of the gland through an incision in its capsule, using the finger to detach it from the capsule and observing great care not to injure the plexus of Santorini, situated at the top of the vesical sphincter, as such injury is likely to induce severe hemorrhage. As suprapubic enucleation is prone to tear the mucosa from the verumontanum, thus exposing the orifices of the ejaculatory ducts to infection, a bilateral vasectomy should always accompany suprapubic prostatectomy. Preliminary drainage is a prerequisite to successful prostatectomy, but may be accomplished in a number of ways according to the needs of the individual patient. Cystotomy employing MacGowan's transverse incision, vesical puncture with Kidd's instrument and the indwelling catheter have all given satisfaction on different occasions.

Primary Tuberculosis of the Parotid Gland.—Bowman and Flin (*Ann. Surg.*, 1932, **95**, 52) state that tuberculosis of the parotid gland is rare and is often mistaken for malignancy, such as syphilis or mixed tumor. Two distinct types are usually found: (1) Chronic or fibroid type, which is encapsulated and may not produce symptoms for months or even years; (2) a type acutely inflammatory, which is diffuse and runs its course in a few days or a week. Tubercle bacilli gain entrance into the parotid gland by one of three ways: Canalicular, hematogenous or lymphatic, with the first being the most common. Symptoms consist of swelling of the gland either as a circumscribed or fluctuating tumor or more diffuse, with an occasional soft spot. The second type is usually adherent, red, tense, shiny and edematous. Pain is a late sign and the glands of the neck are not involved. Diagnosis is likely to be difficult unless it is confirmed by biopsy. Prognosis is good as the affection is purely local. Treatment is purely operative, and even where facial paralysis takes place from injury to the facial nerve, either by disease or operative trauma, there is recovery in most instances.

Traumatic Necrosis of the Liver.—Helwig and Orr (*Arch. Surg.*, 1932, **24**, 136) write that a case of traumatic pulpification of the liver without rupture is reported in which the patient died after 11 days with an extensive nephrosis (general inflammatory involvement of the kidneys). He was extremely jaundiced and had diffuse hemorrhages into the serous cavities. The output of urine was scanty and the blood nitrogen was greatly increased, particularly the creatin which amounted to 25 mg. per 100 cc. The mechanism of renal necrosis is discussed and the histologic renal picture, as well as the clinical course, would seem to favor the theory that some toxin was elaborated in the liver, through hemorrhagic necrosis, which acted directly on the kidney.

THERAPEUTICS

UNDER THE CHARGE OF
CARY EGGLESTON, M.D.,
ASSISTANT PROFESSOR OF CLINICAL MEDICINE, CORNELL UNIVERSITY MEDICAL COLLEGE, NEW YORK CITY,
AND
SOMA WEISS, M.D.,
ASSISTANT PROFESSOR OF MEDICINE, HARVARD MEDICAL SCHOOL, BOSTON, MASS.

Decholin Treatment of Melancholia.—On the theory that certain mental disturbances are more or less closely related to functional disorders of the liver, HARTMANN and WEISSMANN (*Med. Klin.*, 1931, **27**, 1819) employed decholin intravenously in individual doses of 10 cc. in a group of 16 patients suffering from melancholia. They administered from three to ten injections, the average number being 5 per series. In some patients diarrhea, vomiting and elevation of temperature required the interruption of treatment after three or four doses. Eight of the 16 patients showed either subjective or objective improvement as a result of this treatment. In 5 of them this occurred at once after the administration of decholin. In the remaining 3 the improvement did not develop until after the lapse of a few weeks. One patient showed improvement immediately after the first injection but failed to respond to the subsequent ones. The improvement was purely transitory in 3 patients while in 4 it was so pronounced and lasting as to permit their discharge from care. In the remaining 8 patients of the series no benefit was secured. The authors feel that there is some relation between total doses and the results obtained, and that in general five injections are required to give reasonable promise of satisfactory results. However, 2 patients who received nine and ten injections respectively both failed to show satisfactory results. Those patients in whom the melancholia is associated with anxiety states seem to be decidedly more likely to be benefited by decholin than are the purely depressed types.

Quinidin Therapy in the Treatment of Cardiac Irregularities Due to Hyperthyroidism.—Experience with a large number of patients with hyperthyroidism who have been subjected to thyroidectomy constitutes the basis for the conclusions as to the value of quinidin therapy which are presented by ANDERSON (*Ann. Int. Med.*, 1932, **5**, 825). While auricular fibrillation associated with hyperthyroidism tends to disappear following thyroidectomy, the frequency of the spontaneous restoration of normal rhythm varies between 32 and 60 per cent. The postoperative administration of quinidin raises the frequency of return to sinus rhythm to a minimum of 60 per cent and a maximum of 96 per cent. From extensive experience the author concludes that by far the most satisfactory results from quinidin are to be obtained when its administration is begun early, on the third or fourth day postoperative. The usual test doses should precede therapy and the latter should be begun with doses of 0.3 gm. (5 grains) of quinidin administered every 4 hours night and day. This dose may be increased by shortening the interval between administrations to every 3 hours or even to every 2 hours night and day for 1 or 2 days. The proportion of patients who

show idiosyncrasy to quinidin is extremely small in the author's experience and although these patients cannot be continued on the drug this rarely makes them constitute a significant bar to its routine effectiveness in hyperthyroidism.

Experiences With the Use of Metaphyllin Euphyllin, Cheyne-Stokes and Other Forms of Respiratory Disturbances.—On the basis of observations made during the past 8 years with the intravenous administration of metaphyllin for the relief of Cheyne-Stokes respiration and other central respiratory disturbances, VOGL (*Med. Klin.*, 1932, **28**, 9) reaches the following conclusions: That metaphyllin given intravenously in doses varying from 0.24 to 0.48 gm. is the most valuable of all agents for the control and relief of most central forms of respiratory distress. It restores respiration immediately where it has been suppressed by anesthesia for which purpose the large dose should be injected rapidly. Cheyne-Stokes respiration, irrespective of the underlying condition which is responsible for it, is promptly controlled by the administration of small doses, approximately 0.2 gm. given rapidly intravenously just at the beginning of the apneic phase and repeated at a similar point two or three times. That form of dyspnea associated with a sense of oppression but without evidence of circulatory stasis is best relieved by the slow intravenous injection of 0.24 to 0.48 gm. in 10 cc. of distilled water or of 33 per cent glucose solution. Frequently the respiratory distress in cardiac asthma can be much diminished by the same method of administration. The dyspnea of congestive cardiac failure similarly responds very satisfactorily to the injection of a similar dose of metaphyllin combined with salyrgan. Finally, various states of coma such as those associated with narcotic poisoning, cholemia, uremia, etc., are effectively relieved by one or two full doses given intravenously.

Some Actions of Muscle Extract on the Heart Rhythm.—In order to supplement previous observations on the influence of Schwarzmann's extract of skeletal muscle, TURKELTAUB (*Ztschr. f. Kreislaufforschung*, 1931, **23**, 601) made electrocardiographic studies upon a group of healthy young men both before and after the subcutaneous injection of 1 cc. of the extract. He noted a moderate degree of slowing of the heart rate without other changes. Where sinus arrhythmia was present before the administration it persisted or was even increased after administration of muscle extract. Premature beats disappeared shortly after the administration of muscle extract, but this effect was only temporary. In patients showing tachycardia due to auricular fibrillation the extract brought about some slowing of the heart rate which had a slight tendency to persist if its administration were repeated daily. However, the previous administration of digitalis to such fibrillating patients seemed to prevent any further slowing due to muscle extract. One patient showing complete auriculoventricular dissociation with occasional premature beats, developed some increase in the frequency of the latter as the result of the administration of muscle extract.

[EDITOR'S NOTE.—While the observations here recorded are suggestive, a study of the cardiograms reproduced shows that in general the changes observed by the author were insignificant in degree and it is questionable, therefore, whether they have any bearing upon the possible therapeutic value of this extract in the conditions studied.]

PEDIATRICS

UNDER THE CHARGE OF
THOMPSON S. WESTCOTT, M.D., AND ALVIN E. SIEGEL, M.D.,
OF PHILADELPHIA.

Respiratory Failure in Poliomyelitis.—WILSON (*Am. J. Dis. Child.*, 1932, **43**, 1433) found that in 6 children suffering from poliomyelitis who had paralysis of the intercostal muscles and the diaphragm without complications such as pneumonia, the Drinker respirator was ideally efficient in maintaining pulmonary ventilation for long periods. A therapeutic trial of the respirator seems desirable as soon as possible after any reduction of the vital capacity is discovered which is due to weakness of the respiratory muscles. Marked dyspnea or cyanosis should not be waited for as indications for the initiation of treatment. The action of the respirator seemed very effective in 2 children with bulbar paralysis without intercostal involvement who had a sudden complete cessation of respiration after choking. The use of the machine seemed sometimes helpful but was often entirely ineffective in 9 children with bulbar paralysis, without intercostal involvement, who had a disturbed central control of respiration, manifested by irregular breathing. Only 2 of these 9 children survived. The use of the machine in cases with bulbar paralysis without intercostal involvement is not recommended except as an emergency and after every attempt has been made to free the pharynx from all secretions. It was not found possible to foretell accurately the effectiveness of the respirator without therapy trial. Except for moderate emphysema found at autopsy, no evidence of harm resulting from the use of the apparatus was found.

A Study of the Water and Mineral Balances in Epileptic Children.—MCQUARRIE, MANCHESTER and HUSTED (*Am. J. Dis. Child.*, 1932, **43**, 1519) made intensive studies of the water and mineral balances in the case of a severely epileptic girl under experimental conditions in which changes in the state of hydration of the body have been induced by various procedures, other than water restriction. The establishment of a positive water balance was regularly followed by convulsive seizures, excepting one period when intensive phenobarbital therapy was used. Convulsions, which occurred during two of the periods with slightly negative total water balances, actually followed temporary storage of water. Higher level of water exchange does not necessarily favor the occurrence of convulsions if active diuresis or catharsis prevents water retention. During periods of diuresis when no seizures occurred sodium and chlorin were the predominating minerals of the urine. During the alternating periods of rehydration, when seizures occurred, potassium showed a negative balance with a striking increase in the potassium to sodium ratio. During periods of positive water balance the increase in the potassium to the sodium ratio actually manifested itself from 12 to 36 hours before seizures occurred. This apparent leakage of potassium from the cells, which was most marked during a period of sustained pituitary antidiuresis, may indicate an innate weakness in the retaining membranes, presumably of the cells of the central nervous

system. It is possible that abnormal amounts of water and even sodium found entry to the cells at the same time. The data recorded are tentatively interpreted as favoring the view that an inherent defect in the mechanism for regulating permeability of the brain cell membranes is characteristic of the epileptic state. The specific action of the phenobarbital would appear from the limited data presented to be that of maintaining the normal relationships of the electrolytes and water on the two sides of the cell membrane.

Abortive Poliomyelitis.—PAUL, SALINGER and TRASK (*J. Am. Med. Assn.*, 1932, **98**, 2262) made an epidemiologic study of poliomyelitis, in which stress was laid on the problem of so-called abortive poliomyelitis in an effort to define this entity to determine its relative frequency and to bring out methods by which it may be recognized. Common usage of the term abortive poliomyelitis has proved so ambiguous that in order to define the issues in this disease the authors have used the term characteristic minor illness in association with poliomyelitis so that ground may be cleared for a critical, definitive study. The symptomatology of some of these minor illnesses is more or less characteristic but not specific, being essentially that of an acute infection of short duration. Such symptoms as fever, sore throat, headache and vomiting dominate the clinical picture. In a survey of 222 families in each of which 1 or more cases of poliomyelitis had occurred it was found that, coincidentally with the onset of the known case or cases of poliomyelitis, characteristic minor illnesses occurred with a high degree of frequency in the other children of susceptible age. In the age group of 1 to 4 years 39 per cent of children with familial exposure developed a minor illness, and in the age group of 5 to 9 years this incidence was 32 per cent. In 60 control families comparable data were obtained, showing that while the epidemic prevailed, the incidence of similar minor illnesses was about 9 per cent among local children under 10 years of age, who had not been exposed to familial cases of poliomyelitis. In a survey of three communities the ratio of cases of poliomyelitis to these characteristic minor illnesses was in each 1 to 6. Experiments were made in which the poliomyelitic virus was isolated from nasopharyngeal washings in 2 cases of these minor illnesses. Negative results were obtained in 10 others. In both the successful experiments of virus isolation the nasopharyngeal washings were obtained on either the first or the second day of the disease, and three other attempts to isolate the virus during this period proved negative. Strong evidence was developed that these minor illnesses, which are much more frequent than has been suspected, have a common causal relationship with true poliomyelitis.

Vaccine Therapy of Whooping Cough.—WESTENDORFF (*Monatschr. f. Kinderh.*, 1932, **52**, 271) tried this treatment in 15 cases. In intervals of from 2 to 3 days he injected increasing doses of a polyvalent gonococcus vaccine, but there was no noticeable change in the course of the disease. Several months later 20 whooping cough patients were treated with a specific whooping cough vaccine. Only in 2 of these children was the whooping cough influenced favorably. In all of the others the treatment was without benefit. In a case of tuberculosis of the bron-

chial lymph glands, in which pertussis vaccine was given as a prophylactic, it developed nevertheless in 2 weeks. In view of other favorable reports in the literature and considering the 2 cases of his own, the author does not feel justified in considering the vaccine therapy as entirely valueless. He considers that it is a distinct disadvantage that whooping cough is not recognized until it is fully developed. Careful consideration of the history, examination of the hemogram and also bacteriologic examination should be helpful in making an earlier diagnosis. If begun in an earlier stage vaccine therapy may be more beneficial.

DERMATOLOGY AND SYPHILIS

UNDER THE CHARGE OF

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The Intracisternal Serum Treatment of Neurosyphilis.—VIETO (*New Eng. J. Med.*, 1932, **206**, 491) believes that the intrathecal administration of serum in cases of neurosyphilis is much superior to the intraspinal method of Swift and Ellis, since the latter not infrequently produces severe pain and sphincteric weakness. The intracisternal serum treatment has produced very favorable and often rapid changes to normal in the spinal fluid findings in a large series of cases studied at the Massachusetts General Hospital and in private practice. The first evidence of improvement is a diminution in the cell count of the spinal fluid, closely followed by a reduction in the amount of protein and a loss of the higher figures in the colloidal gold reaction, which ultimately becomes negative. The Wassermann reaction on the fluid is the last to respond and may be greatly delayed. It may, however, suddenly become negative. A slight rise in any of the figures is an indication for renewal of the treatment. The therapeutic aim is to bring the spinal fluid to normal and keep it so, a result which the author obtained in a large proportion of cases. The method is apparently of no value in cases of optic atrophy, which progresses to blindness despite serologic improvement, and is futile in frank paresis. Cases showing a paretic formula in the spinal fluid but no clinical evidence of the disease, however, should receive the benefit of a trial of this method, which should be abandoned only if no improvement in the spinal fluid occurs after 2 months of treatment. The author believes that the results obtained from intracisternal serum therapy are better than those obtained by other forms of treatment when used in properly selected cases. Frequently as much improvement ensues in the spinal fluid formula in a few months as might be expected in a few years from intravenous therapy. The

treatment should be given not oftener than once every 2 weeks and should be continued until the spinal fluid has approached normal or is in its normal state. The technique is briefly as follows: Fifteen minutes after an intravenous injection of neoarsphenamin 50 cc. of blood are withdrawn into a 150 cc. Erlenmeyer flask and allowed to stand over night at room temperature without agitation. Twelve hours later from, 20 to 25 cc. of serum can be obtained, which is inactivated at 56° C. for ½ hour and then may be kept a number of days to a week in an icebox. It must be warmed to blood temperature before use. If a portion of the serum not used at a single injection is to be used again within the week, it must be inactivated a second time before injection. The Ayer technique of puncturing the cistern is recommended.

GYNECOLOGY AND OBSTETRICS

UNDER THE CHARGE OF

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Ruptured Endometriomata.—For about 10 years the gynecologic literature has been replete with investigations into the various aspects of endometrial ovarian cysts, or endometriomata, largely due to the interesting and stimulating work of Sampson. While there is still some difference of opinion regarding the exact mode of origin of these cysts, they are sought and identified in many instances in which they were formerly overlooked. One of the complications to which such cysts are liable which has not been generally considered is spontaneous rupture of large cysts. In reporting 3 personal cases and citing another from the literature, NOVAK (*Am. J. Obst. and Gynec.*, 1931, **22**, 826) emphasizes the severity of the abdominal symptoms accompanying such rupture. In 2 of his cases the clinical picture was that of acute appendicitis while in the third a diagnosis of twisted ovarian cyst had been made. In the case quoted from the literature the symptoms suggested ectopic pregnancy or acute peritonitis. He believes that this is a rare complication or else is not recognized as these 4 cases are the only ones he has been able to find. However, one of us (F. B. B.) reported a case of this type in 1928 in which the symptoms suggested a perforated duodenal ulcer. At that time a personal communication with Sampson revealed that he had never seen such a condition as here reported. A case closely simulating a ruptured tubal pregnancy has recently been observed (C. C. N.). The possibility of these accidents should be borne in mind when acute abdominal symptoms develop in cases in which the history and pelvic findings suggest the probability of pelvic endometriosis.

Etiology of Ovarian Pregnancy.—A true ovarian pregnancy is of rather rare occurrence and its etiology is not definitely known, but the conception which WOLLNER (*Am. J. Obst. and Gynec.*, 1932, **23**, 262) advances is interesting. He believes that in the process of physiologic ovulation, after rupture has taken place, a certain amount of force is required to free the ovum from its attachment to the cumulus oöphorus cells and to expel it from within the follicle. The power of this force depends on two factors. The first is the intrafollicular pressure, and the second is the resistance of the surrounding tissue which in turn is dependent upon the thickness of the membranous wall. Any pathologic alteration which involves the tunica albuginea is likely to produce an increased resistance of the follicle wall and affect the mechanism of ovulation causing the extent of the rupture to be smaller. In this event the liquor will not escape with a sudden gush, but will dribble away slowly, thus not having sufficient momentum to free the ovum and flush it into the abdominal cavity. Such a change in the surface of the ovary is often found in chronic oöphoritis and in such cases the ovary often contains numerous follicle cysts which are nothing but unruptured Graafian follicles, which could not rupture because they met too much resistance in the tunica albuginea. Under the above conditions, although there may be a small rupture, the ovum remains in the ovary, and if it becomes fertilized within the follicle it will develop into an ovarian pregnancy.

OPHTHALMOLOGY

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The Importance of Vessel Crossings in the Development of Branch Thrombosis of the Retinal Vein.—According to KOYANAGI'S (*Klin. Monatsbl. f. Augenheilk.*, 1928, **81**, 219) statistics, in 27 cases of branch thrombosis of the retinal veins the superior temporal vein was affected in 22 cases and the inferior temporal vein in 6. No thrombosis of a nasal vein was seen. He believes that the relative frequency of thrombosis in the various venous branches depends on the frequency of arteriovenous crossings in the different quadrants of the retina. Thus, in 124 normal eyes the superior temporal artery and vein were found to cross 194 times, the inferior temporals 80 times, the superior nasals 43 times and the inferior nasals 36 times. Thrombosis always occurs at or peripheral to an arteriovenous crossing. The occurrence of thrombosis at these points is favored by the fact that in many cases, at the crossing, the artery and vein have in part a common wall with closely united adventitia so that changes in the wall or caliber of either artery or vein can narrow the lumen and interfere with the circulation

in the thinner-walled vein. Actual sclerosis of the arterial wall is not a necessary factor. The usual thickening of the arterial wall with increase of elastic tissue which occurs with advancing years may cause sufficient pressure on the vein to initiate a thrombosis. An acute localized inflammatory process in the arterial wall may have the same effect; a venous hyperemia or engorgement may result in thrombosis in the presence of a normal arterial wall. Of the author's 27 patients with branch thrombosis the youngest was 26 years of age, the oldest 84 years and 17 were between the ages of 40 and 60 years; 18 were men and 9 women. In 15 patients the blood pressure was definitely elevated. It was questionably elevated in 4 others. In 8 the Wassermann reaction of the blood was positive. In the early stages of venous thrombosis ophthalmoscopically visible sclerosis in the arterial wall is seldom striking. It is questionable whether the arterial changes demonstrated histologically in the late phases of venous thrombosis are primary or secondary to the disturbance of venous circulation.

OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF

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A Case of Multiple Papillomata of the Larynx With Aërial Metastases to Lungs.—Theobald Smith once said, "It is the natural history of these (infectious) diseases which we lack." And so it is, in no small measure, with neoplastic diseases. Admitting that, generally speaking, morphology is frequently no index to function, experience has taught us that commonly the clinical course of a given tumor can be predicted quite accurately from its histologic structure. When the methods now at our disposal fail to indicate this parallelism, another—and a very valuable—source of information lies in studying the behavior of the tumor cells, particularly their distribution throughout the body and the relationship they bear to contiguous tissues. Convincing evidence of the value of this latter method lies in a case reported by HITZ and OESTERLIN (*Am. J. Path.*, 1932, **8**, 333). Over the span of her second year of life an infant developed consecutively a dry irritative cough, gradual loss of voice and a progressive dyspnea which, on direct laryngoscopy was found to be due to, and relieved by removal of, multiple laryngeal papillomas. The tumor proliferated so rapidly that, despite repeated endoscopic interference during the ensuing year a tracheotomy became necessary. Altogether, ten suspension laryngoscopies were done in a 2-year period, at the end of which the little girl died following improper insertion of the tracheotomy tube. Postmortem examination disclosed that the epiglottis was covered and the larynx and the upper half of the trachea were filled with cauliflower-like papillomatous masses. A remarkable condition existed in the lungs, which contained numerous small cavities studded with millet-seed-sized granules. Some of these pulmonary cavities communicated with bronchioles. Small papillary

plugs often occupied the lumina of bronchioli, the columnar epithelial mucosa of which was found sometimes to be intact. When papillomatous masses occurred in alveoli their origin could be traced from bronchioli. Sections from laryngeal, bronchiolar, alveolar and pulmonary tumor tissue showed the same histologic arrangement—a benign papillomatous architecture. No neoplastic cells were found in the lymphatics. The authors regard their case as an actively growing, histologically nonmalignant primary papillomatosis of the larynx. They believe the evidence justifies an interpretation that fragments detached from the laryngeal growth lodged in the bronchioli, where they became implantation metastases, as well as, by virtue of having been aspirated, "aërial metastases" (Letulle).

RADIOLOGY

UNDER THE CHARGE OF

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Established Actinotherapeutic Modalities in Dermatology.—In the opinion of SCHOLTZ (*Arch. Phys. Ther., X-ray, Rad.*, 1932, **13**, 28) the greatest practical problem of scientific physiotherapy is to counteract the flood of commercial literature luring practitioners into physiotherapy by extravagant therapeutic claims. The greatest danger to scientific physiotherapy in dermatology is presented by the mechanistic tendency promoted by the commercial literature, to be satisfied to clear up the individual skin lesions without any attempts of intelligent interpretation of the dermatosis as a whole. This tendency reduces physiotherapeutic clinicians to the level of physiotherapeutic technicians. No physiotherapeutist is qualified to treat skin lesions unless he has sufficient grounding in dermatologic diagnosis and is competent to administer other dermatologic therapeutic measure if necessary. As a therapeutic weapon in clearing up individual skin lesions, Roentgen ray is much superior to the ultraviolet ray. As a biologic therapeutic agency contributing to the cure of dermatoses, both through systemic and local effects, and from the point of view of general clinical utility to clinical dermatology, the ultraviolet ray is of equal therapeutic value with Roentgen ray and is superior to it in systemic dermatoses. Quartz lamp and carbon arc burners are of identical biochemical and therapeutic capacity and are of equal clinical value. The difference is merely in mechanical and technical details. Full and intense erythema doses of the ultraviolet ray are indicated only in a few types of dermatoses. The majority of therapeutic effects are better obtained with fractional doses. R international units, while physically exact, are not serviceable clinically. McKee's indirect method of measuring Roentgen ray dosage is simple, safe and sufficiently exact for all clinical purposes. Radiologists, as a group, are using in the treatment of skin lesions Roentgen ray of much greater penetration and of a heavier

filtration than is advisable or necessary from a dermatologic point of view. Roentgen ray should be reserved for deep infiltrating dermatoses, granulomata and tumors. Superficial and particularly systemic dermatoses should preferably be treated by ultraviolet ray. The combined and alternate use of fractional doses of Roentgen ray and suberythematous doses of the ultraviolet ray is safe, rational and very effective in a large variety of dermatoses.

Clinical and Roentgenologic Aspects of Ulcerative Colitis.—Ulcerative colitis has been reported from all parts of the world but seems to be more prevalent in the north temperate zone. The disease occurs in every state in the Union. Among predisposing factors, in the opinion of BARGEN and WEBER (*Radiology*, 1931, **17**, 1153), are upper respiratory infections and foci of infection in the teeth, tonsils or gall bladder. Much experimental and clinical evidence suggests that a diplostreptococcus closely resembling the pneumococcus, but of characteristic morphologic and biologic properties, plays an important part in the etiology of the disease. Roentgenologic manifestations of the disease, as seen with the barium enema, are characteristic. In about 20 per cent of cases the disease is confined to the rectal segments; the ampulla is markedly narrowed and exhibits a series of coarse linear striations representing barium in the folds of the strongly contracted ampulla. As the disease progresses the ampulla may become narrow, straight and tubular. In a typical, well-advanced case the colon fills to the ileocecal valve almost instantaneously. The colon is shortened and small in caliber; its course is straight and the angles at the flexures approximate right angles. From a soft, pliable, thin-walled, gently winding tube the colon has become a thick-walled, stiff, straight pipe with a small lumen, somewhat analogous in appearance to a thick-walled, tense sclerotic artery. This picture is not easily confounded with that of any other disease of the colon.

A Clinical Evaluation of Various Qualities of Roentgen and Radium Rays for the Treatment of Advanced Cancer.—From his investigation WIDMANN (*Am. J. Roent. and Rad. Therap.*, 1931, **26**, 729) concludes that equally good clinical results were obtained with long and short wave length Roentgen and radium rays in a series of epitheliomas of the lip. Skin tolerance is greater for short wave length radiations; there is more penetration but apparently less absorption. Skin tolerance increased when different short wave length radiations were combined, and such combinations are recommended because of the improved clinical results.

Roentgen Ray Treatment of Experimental Tuberculosis.—A number of guinea pigs inoculated with tuberculosis were treated with the Roentgen ray by SPIES (*Am. J. Roent. and Rad. Therap.*, 1931, **26**, 716). The progress of the disease was not retarded, and it was indicated, but not proved, that the treatment exerted a deleterious influence. The greater the dosage of organisms the shorter was the subsequent duration of life, but at death the amount of visceral tuberculosis bore no relation to the dosage.

NEUROLOGY AND PSYCHIATRY

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Spinal Cord Changes in Lymphogranulomatosis. — WEIL (*Arch. Neurol. and Psychiat.*, 1931, **26**, 1009) presents a study of 43 cases of Hodgkin's disease published in literature, in which a clinical history is given, with observations made at autopsy or operation. He includes, also 3 case reports of his own. He finds that involvement of the spinal cord begins at the end stage of Hodgkin's disease which may have lasted from 1 to 8 years. The signs of complete spinal cord lesion develop rapidly, after a short period of prodromal signs, from 1 to 6 months before death and within a period of a few days or weeks at the maximum. In 85 per cent of all the cases there was an invasion of the spinal canal by epidural lymphogranulomatous tissue. In 7 per cent which had shown paraplegia clinically, and in which there had been treatment with Roentgen rays, only scar tissue could be demonstrated in the spinal cord, together with severe disease of the retroperitoneal and intrathoracic lymph nodes. In 4 per cent there was an infectious encephalomyelitis and in 4 per cent a syringomyelia was found. In the differential diagnosis of symptoms of disease of the spinal cord in a case of Hodgkin's disease of several years' standing, one should consider: (1) Invasion of the spinal cord by lymphogranulomatous tissue (92 per cent); (2) an infectious myelitis (4 per cent); (3) syringomyelia (4 per cent). Therapy should be directed at early Roentgen ray treatment and laminectomy.

The Hormonal Causes of Premenstrual Tension.—FRANK (*Arch. Neurol. and Psychiat.*, 1931, **26**, 1053) feels that the continued circulation of an excessive amount of female sex hormone in the blood may in labile persons produce serious symptoms, some cardiovascular, but the most striking definitely psychic and nervous. He divides the women possessing these premenstrual disorders into three groups: (1) Those with minor disturbances including increased fatigability, irritability, lack of concentration and attacks of pain; (2) those in whom the symptoms complained of are of sufficient gravity to require rest in bed for one or two days and in whom pain plays the predominant rôle; (3) those in whom grave systemic disorders manifest themselves. He presents a series of 18 cases which fall into the above grouping in whom he has succeeded in relieving the distress. The treatment he recommends is dependent upon the severity of the disorder and consists of calcium lactate, theobromin sodiosalicylate, magnesium citrate or Roentgen-ray to the ovaries.

The Histopathology of Triorthocresyl Phosphate Poisoning: The Etiology of So-called Ginger Paralysis (Third Report).—SMITH and LITTLE (*Arch. Neurol. and Psychiat.*, 1931, **26**, 976) present a study of: (*a*) Histopathology of spinal cord and peripheral nerves of 6 cases of paralysis due to adulterated fluid extract of ginger in man. The lesions observed were characterized by some involvement of the anterior horn cells and in most cases by considerable fatty degeneration of the white substance of the spinal cord. The changes in the peripheral nerves were a well-marked fragmentation and fatty degeneration of the myelin sheath, which involved groups of fibers throughout the nerve trunks. (*b*) Similar studies of dogs, monkeys, chickens, calves and cats, using triorthocresyl phosphate. In these animals the lesions observed were essentially similar to those produced by the adulterated fluid extract of ginger.

Plantar Reflexes in Normal Adults.—DAVIDSON (*Arch. Neurol. and Psychiat.*, 1931, **26**, 1026) presents the results of an examination of the plantar reflexes of 160 normal adults, under arbitrarily chosen standard conditions. These conditions were: Patient supine, head away from the side stimulated; knee extended; patient distracted; stimulus made with a McCouch stimulator at an intensity of 165 gm.; stroke made on the fibular side of the foot, starting at the heel, moving deliberately along the sole to the end of the foot. He decided that in adults there is no one type of response that can be considered the normal plantar reflex. In most cases all the toes flex, but extension of the toes, even of the big toe, is compatible with a normal motor system. Isolated extension of the big toe with fanning of the other toes does not occur in normal adults. He feels that no theory has adequately explained the plantar reflex; no such theory can be accepted unless it accounts for (*a*) the infantile Babinski sign, (*b*) the fact that the response in human adults is usually flexion and (*c*) the clinical Babinski sign of disease of the pyramidal tract.

Injury and Repair Within the Sympathetic Nervous System: I. The Preganglionic Neuroses.—TOWER and RICHTER (*Arch. Neurol. and Psychiat.*, 1931, **26**, 485) present a study of the regeneration of sympathetic function in 26 adult cats in which the preganglionic sympathetic nerve fibers were cut on the right side just before their entry into the stellate ganglion. "The effects of the operation were: (1) The immediate elimination of the spontaneous waves in skin potential and of the galvanic skin responses. (2) An immediate increase in electrical skin resistance. The resistance of the skin reached a peak many times the maximum normal figure between the second and fifth days after operation, and thereafter fell slowly and with fluctuation. Between the third and seventh weeks, as skin resistance again approached a normal figure, the action currents of the skin reappeared. This reappearance was taken as the time of reconstitution of the connection between the central nervous system and the periphery. It averaged 28 days. Evidence of some form of function of the synapse is noted several weeks before this date. The observations on sweating made at the same time indicate that the galvanic skin reflex response is a far more delicate test for the presence of sympathetic innervation than gross observation of the activity of the sweat glands.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF
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Experimentally Produced Lesions of the Liver.—Studies of experimentally produced lesions in liver were undertaken by BOLLMAN and MANN (*Ann. Int. Med.*, 1931, **5**, 699). These authors found that most of the hepatic lesions met with in man could be produced in the experimental animal. Complete removal of the liver results in hypoglycemia with loss of power to form sugar and urea. Amino and uric acids are not destroyed and progressive symptoms of acute hepatic insufficiency with coma, convulsions and death ensue. Partial removal of the organ demonstrated that less than 20 per cent of normal liver substance was sufficient to maintain life. Emphasis is placed upon the great regenerative power of hepatic tissue, partial removal of the organ at repeated intervals showing that the liver is capable of restoration of more than 100 per cent of its weight without signs of hepatic deficiency. This regenerative ability is greatly reduced or absent in obstructive jaundice, in marked cirrhotic changes or where the portal blood supply has been reduced. Ligation of the common duct leads to development of varices, intestinal hemorrhages and ascites. Duodenal ulcer is frequent. Cholecystenterostomy gave rise to a low-grade infection of biliary ducts with production of an infective type of cirrhosis. Repeated administration of carbon tetrachlorid and tetrachlorethane produced a picture resembling portal cirrhosis; with more extensive injury a subacute yellow atrophy is produced. Alcohol greatly increased the toxicity of several toxic substances. Signs and symptoms of hepatic insufficiency only supervene when the organ has suffered very profound alterations, most of the liver function tests failing to show any pathologic change until this has occurred. Satisfactory correlation between the amount of liver damage and the degree of retention of bromsulphthalein was usually, although not invariably, found. The ascites which occurs spontaneously in extensive experimental cirrhosis and obstructive jaundice of long duration may be produced by feeding the animal meat or meat extractives. The disappearance of ascites, which occurs when these substances are withdrawn is facilitated by large amounts of carbohydrate. Salt appears to play no part in the production of ascites and the great protective value of carbohydrate against hepatic injury is emphasized.

Tumors of the Islands of Langerhans and Hypoglycemia.—Five cases of tumors of the islands of Langerhans have been reported by SMITH and SIEBEL (*Am. J. Path.*, 1931, **7**, 723). Four of these cases were observed at autopsy while in 1 the tumor had been successfully removed by surgical operation. Two of the cases presented a definite history of hypoglycemia, 1 a questionnaire history, 1 had no symptoms

referable to the pancreas and in 1 a mild diabetes was present. The authors consider all their cases as adenomas rather than carcinomas or hypertrophied islet tissue. In some of the tumors the cells contain abnormal secretory granules while in others they are absent. It is believed that tumors producing hypoglycemia are composed largely of beta cells. In the authors' cases the islets in the remainder of the pancreas are of normal size and show a normal granular content. The activity of the normal islets does not seem to have been depressed by the excess of insulin produced in the tumor. The latter is not controlled by the normal mechanism governing insulin production and may produce hypoglycemia even when small. The occurrence of mild diabetes in 1 case suggests that the low sugar tolerance is dependent upon some developmental defect of the islets which also is responsible for the growth of the adenoma.

On the Structural Changes of the Tunicæ in Varicose Veins.—From a study of tissue removed at operation MAGGIO (*Lo Sperimentale*, 1931, **85**, 185) concludes that varices occurring in the saphenous vein and pampiniform plexus may show two distinct types of lesions. In the first there is primarily degeneration of the muscle fibers of the media. Accompanying this is an irregular compensating increase in the elastic fibers and laying down of connective tissue in the middle and outer coats; this causes distortion and often narrowing of the lumen of the vessel. This newly formed tissue is also liable to undergo hyalin degeneration, so that when stasis is superimposed thinning of the wall and irregular dilatation take place. The intima plays very little part in the process, although in the advanced stages the whole vessel wall is transformed into a more or less clear substance, showing no semblance of cellular structure. In the second type it is the intima which is the seat of the initial lesion. An overgrowth of the subendothelial connective tissue in a diffuse or patchy manner and splitting of the internal elastic lamina into many layers causes narrowing of the lumen. As time goes on the elastic tissue of the media increases and also tends to invade the adventitia. Finally, the new tissue in all three layers degenerates, so that there are left areas of a thin, hyalin material, interspersed with portions in which the process is still active. Both varieties of change are considered to be caused by a toxic process, possibly associated with deranged endocrine function.

The Morbid Anatomy of the Diaphragm.—A study of the morbid anatomy of the diaphragm has been made by LUCKÉ (*Ann. Int. Med.*, 1931, **5**, 750) and a series of 164 cases has been reviewed. In this series carcinoma occurred in 14 cases, sarcoma in 3 and hypernephroma in 1. Carcinoma of the diaphragm, most often arising primarily in stomach, spreads throughout the muscle bundles from the subserous lymphatic channels, giving rise to a diffuse flat nodular infiltration with usually a considerable destruction of tissue. Tuberculosis, which was present in 35 cases, most frequently occurred as a serositis but also as isolated or conglomerate tubercles. The peritoneal surface was more often involved, even when the primary focus was above the diaphragm; adhesions to adjacent organs were common and much destruction of muscle sometimes occurred. Acute diaphragmitis was present in 25

cases with inflammation of both serous surfaces and in each case involvement of the muscle in either a degenerative or inflammatory process. The latter which most commonly was associated with pneumonia presented a picture of a true myositis with edema, polymorphonuclear infiltration and the formation of fibrin, later going on to organization and scar formation leading to inference of muscular contraction. Hydropic degeneration and Zenker's hyalin degeneration were frequently seen and cloudy swelling and fatty degeneration often occurred. The author believes that these processes commonly occurring in pneumonia may play an important part in bringing about respiratory failure in that disease.

HYGIENE AND PUBLIC HEALTH

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Scarlet Fever Streptococcus Antitoxin in the Treatment of Scarlet Fever.—VELDEE, STEVENSON and MITCHELL (*Pub. Health Rep.*, 1931, **46**, 3023) made a most carefully controlled study of the therapeutic value of two samples of scarlet fever antitoxin. The discussion which gives briefly the results of the work is as follows: We have attempted to present in this report a detailed analysis of each case included within our study, the purpose being not only to note the more obvious clinical variations in our three groups but also to analyze the records more minutely with a view to determining wherein, if at all, scarlet fever streptococcus antitoxin fails to accomplish its purpose. That the antitoxin has a specific neutralizing effect on the toxin *in vivo* is indicated by the decrease in the duration of the rash, by a change in the character and extent of the desquamation, and by a reduction in the number of complications. That it failed to neutralize completely the damaging effect of the toxic substances produced by the scarlet fever infection is suggested by the failure of the rash to disappear promptly, by the continuation of the fever and by the appearance of complications in a certain number of serum-treated cases. These failures may have been caused by (*a*) too small a therapeutic dose, (*b*) an improper method of administration, (*c*) administration too late in the disease, or (*d*) an inadequacy of antitoxin to neutralize all of the toxic substances elaborated in this disease. It is our belief, and this is confirmed by other clinicians and by investigations of the action of scarlet fever toxin, that early administration of antitoxin and its rapid dissemination throughout the body of the patient are essential; the toxin being elaborated very early in the disease and effecting its tissue damage without delay. The probability of serum sickness must also be weighed in the use of scarlet

fever antitoxin. However, the frequency of this complication cannot be attributed entirely to a peculiar property of an antistreptococcic serum itself, since it was shown that previous sensitization to horse serum played an important rôle in its incidence. With the introduction of a more effective method of producing active immunity against diphtheria by the use of toxoid instead of toxin-antitoxin mixture, there will be a corresponding reduction in the percentage of children sensitized to horse serum. There is also the fervent hope that ultimately an improved method of manufacture will become available so that the volume of the therapeutic dose of scarlet fever streptococcus antitoxin may be greatly reduced, which in itself will minimize the probability of serum sickness.

Changes in Ionic Content of Air in Occupied Rooms Ventilated by Natural and by Mechanical Methods.—Intensive investigations have until now failed to discover the specific cause of deadness, or lack of a stimulating quality, in the air of occupied rooms, even when temperature and humidity are controlled, as contrasted with the air of the open country. Proponents of the open air treatment ascribe this quality of freshness to a vital principle which is lost when air is brought indoors, particularly when ventilation is effected by mechanical means. In recent years, since the carbon dioxid, oxygen and crowd poison theories have become obsolete, ionization has been suggested as the air-soluble vitamin, but it has not yet been identified. The virtues of artificially ionized air have been extolled on purely theoretical grounds, with no scientific confirmation whatever. YAGLOU, BENJAMIN and CHOATE (*J. Soc. Heating, Piping and Air Conditioning*, October, 1931, p. 865) have studied the problem of ionization in relation to ventilation and health. Their paper deals largely with fundamental changes in the ionic condition of the air in occupied rooms ventilated by natural and by mechanical methods, and with the influence of various air conditioning processes upon the ionic content of air. A series of experiments was carried out in rooms, both occupied and unoccupied: (1) With no ventilation; (2) with window-gravity ventilation; (3) with mechanical ventilation, in order to determine the extent to which the number of small ions is affected by respiration and transpiration and by modern air-conditioning methods. In contract with the prevailing belief, the ionic content in unoccupied heated rooms did not differ much from that out of doors, and in cold weather it was often higher, owing probably to a temperature effect. In occupied rooms there was a marked decrease in both positive and negative ions. Immediately after the occupants assembled the ionic content of the air fell abruptly to a very low value, which was maintained until the occupants left the room. Both positive and negative ions began to rise again as soon as the people departed. The minimum supply of outdoor air required to maintain normal ionic content in a crowded room was found to be prohibitively high (160 cfm. per person). With the usual air supply of 30 cfm. per person, the ionic content did not seem to differ greatly from that with no ventilation at all. On the other hand, it was possible by means of artificial ionization to control both the quantity and the quality of ions at any desired concentration up to 10,000 ions per cubic centimeter, with or without ventilation. Mechanical ventilation reduced the ionic content from

0 to 30 per cent by diffusion and adsorption to metal conductors. Heating the air by means of a central fan system increased the ionic content, and cooling by similar methods decreased it. The usual method of washing humidifying or dehumidifying by means of water sprays, deprived the air of all small ions, and produced a great number of large negative ions, or condensation nuclei, by the well-known Lenard effect. Recirculation reduced both positive and negative ions by diffusion and adsorption to metal conductors.

Antitoxin Immunity to Diphtheria in Relation to Tonsillectomy.—WHEELER, DOULL and FROST (*Am. J. Hyg.*, 1931, **14**, 555) state that the conditions of observation in the two Baltimore groups, of school-children and students, respectively, are not entirely comparable to those obtaining in the most significant of the groups studied by Schick and Topper. The latter cite observations on children known to have been Schick-positive immediately before tonsillectomy and retested usually within 6 months thereafter, while the Baltimore records for children who have undergone tonsillectomy refer to Schick tests performed some years after the operation. Hence, a possible explanation of the discrepancy between the results is that the negative reactions which Schick and Topper found developing so commonly and quickly after tonsillectomy may have been temporary, tending to revert within a few years to positive reactions. This explanation does not seem probable, for although reversions from Schick-negative to Schick-positive reactions are not very uncommon, all the evidence at present available indicates that in any considerable group of children under natural conditions, the tendency is regularly toward a progressive increase, year by year, in the proportion of negative reactors. Therefore, if tonsillectomy in the groups observed in Baltimore had tended to stimulate the development of antitoxic immunity at anything like the rate indicated by Schick and Topper's observations, one would expect that the effect would still be clearly demonstrable after the lapse of several years. In view of this wide divergence, the need for further observations on the subject is obvious.

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